MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

Date: January 14, 2005

Subject: Clinical Review of New Biologics License Application STN# 125089—Menactra
Date of submitted application: 12-18-03

Amendments reviewed: 125089/0 (clinical, crf, other and label sections),
125089/1, 125089/3-5, 125089/7-8, 125089/15, 19, 22

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Product: Meningococcal (Groups A,C,Y,W135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine
Sponsor: Aventis Pasteur, Inc.

BLA review committee:

Carl Frasch	Chairperson
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1.0 General Information

1.1 Content: Clinical Review of New Biologics License Application (BLA)

1.1.1 BLA #: STN# 125089

1.1.2 Date BLA submitted: 12-18-03

1.1.3 Clinical Review completed: 01-14-05

1.2 Product name

1.2.1 **Generic name:** Meningococcal (Groups A,C,Y,W135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine

1.2.2 **Proposed trade name:** Menactra

1.2.3 **Product composition:** 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 W135
- 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 Sponsor: Aventis Pasteur Inc.

1.4 Pharmacologic category: Vaccine

1.5 Proposed indication: Active immunization of adolescents and adults for prevention of invasive disease caused by *Neisseria meningitidis* serogroups A, C, Y and W135

Target age group: 11-55 years old

1.6 Dosing regimen and Route of administration: Single dose, intramuscularly

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3.0 Introduction and Background

3.1 Epidemiology of meningococcal infections in adolescents and adults

Meningitis and meningococcemia are common manifestations of invasive disease due to *Neisseria meningitidis* (*N. meningitidis*). Other clinical presentations of meningococcal disease include pneumonia and occult bacteremia. During 1991-1998, increased numbers of meningococcal cases were reported in the United States among persons aged 18-23 years old ($1.4/10^6$ population), compared with the general population ($1.1/10^6$ population).[1] In 2003, preliminary data indicate that the incidence of meningococcal disease in this age group was an estimated $1.0/10^6$ population, and remains above the general population ($0.5/10^6$ population). [2] The highest rate of meningococcal disease continues to occur in children younger than one year of age. Approximately 50% of meningococcal disease in this age group is due to serogroup B.[1,2]

The epidemiology of meningococcal disease in the United States has changed in the last 15 years. The proportion of meningococcal disease due to serogroup Y increased from 2%, during 1989-1991, to 30% during 1992-1996, and to 37% in 1997-2002. [2,3] The epidemiology of meningococcal disease also reflected an increased number of reported localized serogroup C outbreaks. Eight outbreaks occurred during a two-year timeframe [1991-1993], compared with 13 outbreaks in the previous decade [1980-1990].[4] Cases of serogroup W135 meningococcal disease were also reported in association with an outbreak among travelers returning from the Hajj, in 2000-2001.[5] The distribution of meningococcal isolates for serogroups C, Y, and W135/other, during 1997-2003, was 24%, 28%, and 14%, respectively.[2]

The mortality rate due to meningococcal disease overall is 7 to 19%, and for meningococcemia, 18-53%. The case-fatality rate due to serogroup W135, C and Y, during 1992-1996 was 21%, 14%, and 9%, respectively.[3] Despite susceptibility of *N. meningitidis* to many antibiotics, approximately 10-20% of individuals with meningococcal disease experience permanent sequelae (e.g. limb loss, neurosensory hearing loss, cognitive deficits, seizure disorder).[6-8]

3.2 Immune Correlate: Serum Bactericidal Antibody

The role of bactericidal antibody in protection against meningococcal disease has been demonstrated in several ways. In studies conducted in the 1960's, military recruits who were susceptible to meningococcal group C disease had no detectable serum bactericidal antibody.[9,10] The absence or presence of functional antibody was determined with a serum bactericidal assay (SBA) using an intrinsic human complement (HC) source. A positive result indicated the presence of complement mediated anti-meningococcal group C antibody, and was a qualitative measurement at an estimated dilution of 1: 4. Secondly, the highest incidence of meningococcal disease was observed to occur in infants 6-12 months old, an age at which the prevalence of bactericidal antibody was lowest.[9] The gradual increase in prevalence of bactericidal antibody correlated with decreased age-related incidence of meningococcal disease. [10] Third, individuals deficient in serum complement components C5, C6, C7 or C8 were found to have increased susceptibility to meningococcal disease, and have repeated meningococcal infections.

Since *in vitro* measurement of bactericidal antibody was indicative of functional activity *in vivo*, and serum bactericidal antibody was considered to be a reliable predictor of vaccine effectiveness. Clinical efficacy of monovalent meningococcal A and C polysaccharide vaccines, and combined meningococcal AC polysaccharide vaccines were confirmed in large-scale field trials.

3.3 Rationale for selected formulation

Menactra contains capsular polysaccharides of *N. meningitidis* serogroups A, C, Y and W-135, each of which are conjugated to diphtheria toxoid.

In general, benefits of a conjugate vaccine include induced T-dependent antibody response, affinity antibody maturation, immunologic memory and consequent enhanced antibody response, and herd immunity. These characteristics have recognized with *H. influenzae* type b and pneumococcal conjugate vaccines. The immunogenicity data included in this license application support demonstration of short-term protection one month following Menactra vaccination, compared to Menomune®. Studies demonstrating long-term protection against the vaccine serogroups are currently ongoing.

3.4 Regulatory background

3.4.1 Basis for Licensure

The licensure of Menactra is based on the following aspects:

- Demonstration of efficacy: immunologic equivalence to Menomune® A/C/Y/W135, a U.S. licensed meningococcal polysaccharide vaccine.
- Demonstration of safety compared to Menomune® A/C/Y/W135
- Demonstration of lot consistency

3.4.2 Use of Immunologic Correlates for Licensure of Meningococcal Vaccines

Demonstration of efficacy, inferred from immunogenicity data, was an approach used as a basis for Menomune®. The primary measure of immune response was the proportion of participants who achieved a four-fold or greater increase in serum bactericidal antibody to each serogroup. Use of immunologic correlates was recently discussed by the vaccine advisory committee, in September 1999,[11] as an approach for approval of new meningococcal conjugate vaccines. The outcomes of the Vaccines and Related Biological Products Advisory Committee Meeting, held on September 15, 1999, which pertain to the proposed age group in this biologics license application, are as follows:

- Use of an immunologic correlate to determine effectiveness of new meningococcal conjugate vaccines is acceptable
- In individuals for which the current meningococcal polysaccharide vaccine is licensed, serum bactericidal antibody can be used as a predictor of vaccine efficacy

3.4.3 Abbreviated Regulatory Timeline

The application was reviewed within an established standard timeframe.

05-23-97	IND filed
09-15-99	Vaccines and Related Biological Products Advisory Committee Meeting: Use of immunologic correlates for the demonstration of efficacy of meningococcal conjugate vaccines
09-29-00	Comparative safety and immunogenicity study started
04-16-01	Expanded safety study started
03-02-03	Lot consistency study completed
12-18-03	BLA submitted
	Pre-approval inspections:
03-05-04	BiMo Inspection sites selected
08-02-04	Facilities Inspection begin
09-22-04	Vaccines and Related Biological Products Advisory Committee Meeting

4.0 Chemistry, Manufacture and Controls

4.1 Product composition

Menactra is formulated as a liquid in a single-dose vial. Each 0.5ml dose contains 4ug of polysaccharide (PS) for each of the serogroups A, C, Y and W135. Each PS is conjugated to

diphtheria toxoid; the total diphtheria toxoid protein content per dose is 48ug. Other ingredients contained in the vaccine include [redacted] mg sodium phosphate and [redacted] mg sodium chloride. The vaccine contains neither an adjuvant nor preservative. Please see Appendix 2 for the batch numbers of vaccine used in each clinical trial.

4.2 Product manufacture

The purified capsular PS contained in Menactra is manufactured by the same process as the capsular PS used in the production of Menomune® A/C/Y/W135. The PSs were prepared in Swiftwater, PA [PLA 81-105; STN 103926-0]. The carrier protein, diphtheria toxoid, is manufactured by the same process as the diphtheria toxoid component contained in Tripedia® [PLA 90-0353; STN 103922-0].

4.3 Control vaccine

The active control vaccine implemented in studies MTA-02, MTA-04, MTA-09 and MTA-14 is Menomune® A/C/Y/W135. Each 0.5 ml dose contains 50ug of "isolated product" from each serogroup, and is formulated as lyophilized powder in a single-dose vial. Lactose is added as a stabilizer (2.5-5 mg). Following reconstituted with sterile water, the vaccine appears as a clear, colorless, liquid.

Menomune® A/C/Y/W135 is administered subcutaneously. Since the route of administration for Menactra and Menomune® A/C/Y/W135 differed, study personnel who administered the vaccine were different from the personnel collecting the safety data. Please see Appendix 2 for the batch numbers of vaccine used in each clinical trial.

4.4 Laboratory Methods

Anti-Meningococcal Antibody Determination by Serum Bactericidal Assay

Functional antibody activity to each serogroup was determined using a serum bactericidal assay. The assay was performed at Aventis Pasteur Inc. according to an adaptation of the CDC method recommended by the WHO Expert Committee of the Department of Vaccines and Biologicals. [12,13] Meningococcal serogroup strains F8238 (Group A), C11 (Group C), 3021 (Group Y), and 2515 (Group W135) were obtained from the CDC. Serum from CDC donor R21654-3430107 is used as a reference standard. [redacted] dilutions of test sera were prepared in [redacted] Serogroup specific meningococcal bacteria and baby rabbit complement were added to the serum dilutions and allowed to incubate. After the incubation period, [redacted] Bacterial colonies present in the wells were counted, and the endpoint titer determined by the reciprocal serum dilution yielding > 50% killing, compared to the mean of the complement control wells. The lower limit of detection for this assay, using rabbit complement, is an antibody titer of 8.

5.0 Animal Pharmacology and Toxicology Studies

Study 407/128: Comparative evaluation of maternal Ig transfer in rats, mice and rabbits
Study 407/158: Developmental toxicology study in mice
Study 407/166: Toxicity study to evaluate a one and two dose vaccination regimen, administered intramuscularly

Please refer to the review of Dr. Hanan Ghantous.

6.0 Clinical Studies- Overview

The license application included safety and immunogenicity data from six clinical studies and one supplemental study. Safety data from two additional supporting studies was also included.

Study Protocol #	Description	Study Population	Number of Participants Enrolled		
			Total (N)	Menactra	Menomune**
Pivotal Studies					
MTA-02 USA	**Safety + Immunogenicity**	**11-18 years**	**881**	**440**	**441**
MTA-04 USA	**Safety**	**11-18 years**	**3242**	**2270**	**972**
MTA-09 USA	**Safety + Immunogenicity**	**18-55 years**	**2554**	**1384**	**1170**
MTA-11 USA	**Concomitant vaccine: Typhim Vi eval.**	**18-55 years**	**945**	**Gr A 469 Gr B 476**	**0**
MTA-12 USA	**Concomitant vaccine: Td evaluation**	**11-17 years**	**1021**	**Gr A 509 Gr B 512**	**0**
MTA-14 USA	**Lot consistency**	**18-55 years 26-55 years**	**2040**	**1582* 458**	**0 458**
Supplemental Studies- adults					
603-01 USA	**Dose escalation, Safety, Immunogenicity**	**18-55 years**		**30****	**0**
Total Number of Enrolled Participants Aged 11-55 years old:			**N 10, 713**	**Menactra: 7672**	**Menomune**: 3041**

*MTA-14: Menactra [n= 533 planned per lot]; [n= 527 enrolled for lots 1&3 (each), n= 528 enrolled for lot 2]
**603-01: 30 adult participants received a 4ug dose, the dose selected for the final formulation. Sixty additional adults were enrolled and received a 1 or 10ug Menactra dose (n= 30 subjects/ dose).

Other supporting studies:

- Study 603-02, a safety and immunogenicity study in healthy U.S. children 2-10 years old
- Study MTA-08, a large scale safety study in healthy U.S. and Chilean children 2-10 years old

7.0 Clinical Studies

7.1 Pivotal Clinical Studies

7.1.1 Study MTA-02: A Comparative Trial of the Safety and Immunogenicity of One Dose of an Experimental Tetravalent (A, C, Y, and W-135) Meningococcal Diphtheria Conjugate Vaccine versus Menomune® A/C/Y/W-135 in Healthy Adolescents in the U.S.

7.1.1.1 Objectives

- Primary objective: To describe and compare the bactericidal antibody response to serogroups A, C, Y, W135, using baby rabbit complement (SBA-BR), among healthy adolescents immunized with Menactra with the SBA-BR responses following vaccination with a licensed meningococcal polysaccharide vaccine.

- Secondary objective: To describe and compare the safety profile for Menactra and Menomune® recipients.

- Other objectives:
  - ✓ To describe and compare the SBA-BR response to each serogroup pre- and 28 days post-vaccination for Menactra and Menomune® recipients.
  - ✓ To compare serogroup-specific IgG and IgM antibody levels pre- and 28 days post-vaccination in a subset of Menactra and Menomune® recipients.
  - ✓ To describe and compare the proportion of participants who achieve seroconversion 28 days following a single dose of either Menactra or Menomune®.
  - ✓ To describe any relationship between post-vaccination reactogenicity and elevated pre-vaccination SBA-BR titers to each serogroup among recipients receiving either Menactra or Menomune®.

7.1.1.2 Design

The study was a randomized, modified double blind (different routes of administration), multi-center, active-controlled trial. Since the route of administration for the study vaccine differed from the control vaccine, study personnel who administered the vaccine differed from the personnel collecting the safety data. The control group received Menomune® A/C/Y/W-135. Participants were randomized in a 1: 1 (Menactra: Menomune®) ratio.

Study Period: September 29, 2000 to October 30, 2001

7.1.1.3 Protocol

7.1.1.3.1 Population

The study was conducted at eleven study centers in the United States.

Inclusion criteria:

- Healthy
- Age ≥11 years and <19 years old at the time of vaccination
- Informed consent obtained

Exclusion criteria:

- Serious chronic disease (i.e. cardiac, renal, neurologic, metabolic, rheumatologic etc.)
- Known or suspected impairment immunologic function
- History of documented invasive meningococcal disease or previous meningococcal vaccination
- Receipt of immune globulin or other blood products within the previous 3 months, injected or oral corticosteroids within 6 weeks prior to the administration of the study vaccine
- Administration of a vaccine other than the study vaccine within 28 days of enrollment
- Antibiotic therapy within 72 hours prior to vaccination
- Known or suspected hypersensitivity to any vaccine component
- Enrolled in another clinical trial
- Any condition which, in the opinion of the investigator, would pose a health risk to the participant
- Unable to comply with scheduled visits or study procedures
- For females, a positive or equivocal urine pregnancy test result on the day of vaccination

Reasons for deferring vaccination

- Acute medical illness, with or without fever, within the previous 72 hours. Fever was defined as an oral temp $\geq$38.0C.

7.1.1.3.2 Vaccine administration

Each group received a single dose of vaccine. Menactra was administered intramuscularly, and the control vaccine, Menomune®, was given subcutaneously.

7.1.1.3.3 Endpoints

Primary Endpoint:
The proportion of participants with a $\geq$4-fold rise in SBA-BR titer for *N. meningitidis* serogroups A, C, Y and W-135 28 days post-vaccination, compared to baseline.

Secondary Endpoint:
The proportion of participants with a least one solicited systemic reaction reported as severe during the 7-day period following vaccination.

7.1.1.3.4 Surveillance

Monitored parameters:
Safety: Study participants were monitored for immediate reactions 30 minutes post-vaccination, and for local and systemic reactogenicity during the 7 days following vaccination. Pre-specified adverse events included localized reactions (erythema, swelling, induration, pain) and systemic symptoms (fever measured by oral temperature, headache, fatigue, malaise, anorexia, vomiting, diarrhea, and rash). These events were recorded on a diary card, and also collected by study personnel through telephone interview eight days after vaccination. Other non-serious, unexpected adverse events were obtained by telephone interview eight and twenty-eight days after vaccination.

Information regarding chills, arthalgia and arthritis were not collected during this study, since more than 50% of study participants had already been enrolled at the time a revised protocol was requested. The presence of rash was assessed qualitatively, but prompts for additional details were not included on the case report form.

Serious adverse events were reported and recorded during the 6-month study period following vaccination. A serious adverse event was defined as any untoward medical occurrence resulting in death, life-threatening experience, inpatient hospitalization, prolonged existing hospitalization, persistent or significant disability/incapacity, or a congenital anomaly/birth defect. In addition to these events, visits to

an emergency room, or unexpected visits to an office physician were collected via scripted telephone interview.

Efficacy (Immunogenicity): Serum samples were obtained pre- and 28 days post-vaccination. For all study participants, bactericidal antibody response was determined with an assay using baby rabbit complement. The lower limit of detection for the assay was an antibody titer of 8. In a subset of 160 adolescents (80 subjects/group), serogroup-specific IgG and IgM antibody were measured by ELISA. All assays were performed at Aventis Pasteur, Inc.

7.1.1.3.5 Statistical plan

Primary Hypothesis:
To demonstrate that 28-days after vaccination, Menactra is non-inferior to Menomune® by proportion of participants with a ≥4-fold rise in SBA-BR titer for *N. meningitidis* serogroups A, C, Y and W-135.

This hypothesis would be supported if the upper bound of the one-sided 95% confidence interval (CI) of $p_{\text{Menomune®}} - p_{\text{Menactra}}$ is less than 0.10, where p represented the proportion of participants with a ≥4-fold rise in SBA-BR titer as compared to baseline, for each serogroup. Planned enrollment of 812 participants, with resultant 732 evaluable study subjects (366 subjects/group) provided 90% power, overall, to achieve the primary hypothesis for serogroups C, Y and W135. All tests of the primary hypothesis were conducted at the 0.05 significance level. The primary hypothesis was modified during the trial to include a non-inferiority comparison for serogroup A. Hence, the sample size and power calculations do not include hypothesis testing for this serogroup. The primary analysis was based on data generated from the per-protocol population.

Per-protocol population for immunogenicity:
The per-protocol population included all eligible participants who received one dose of vaccine according to the treatment assignment, who complied with scheduled visits for blood specimens, and for whom a sufficient quantity of paired sera was available for analysis.

Intent-to-treat population for immunogenicity:
The intent-to-treat population consisted of all enrolled participants who received one dose of vaccine and underwent the first blood draw. Analyses were performed according to the vaccine received.

For analysis purposes, if the SBA-BR antibody titer to any serogroup was reported below the limit of detection, the antibody titer assigned was a value equal to the limit of detection. ITT analysis for the primary endpoint was considered exploratory. These results were not included in the license application, but are anticipated to be submitted as an appendix to the final study report.

Secondary Hypothesis:
To demonstrate that the relative frequency of severe systemic reactions in Menactra recipients is non-inferior to the relative frequency of severe systemic reactions among Menomune® recipients.

This hypothesis would be supported if the upper bound of the two-sided 90% CI of $p_{\text{Menomune®}} - p_{\text{Menactra}}$ is less than 0.10, where p represents the proportion of participants with at least one severe systemic reaction during Days 0-7. Hypothesis testing was conducted at the 0.05 significance level.

Additional hypothesis testing of the secondary endpoint, with two-sided 95% CI, was also described. All rashes occurring during the first 7 days after vaccination were designated, for the purpose of analysis, as a severe solicited systemic reaction. Since the nature and severity of a rash were difficult to categorize for the vaccine recipient, all rashes were designated as severe in an effort by the sponsor to prompt the investigator for more detailed rash characteristics.

Intent-to-treat population for safety:
The intent-to-treat population consisted of all participants who received one dose of vaccine and for whom safety information was available. Analyses were performed according to the vaccine received.

7.1.1.4 Results

7.1.1.4.1 Population

A total of 881 (Menactra n=440, Menomune® n= 441) adolescents were enrolled, and 871 (Menactra n=436, Menomune® n= 435) individuals completed the study.

Safety population:
The intent-to-treat population for safety included 881 participants (Menactra n=440, Menomune® n= 441). Ten participants (Menactra n=4, Menomune® n= 6) were not available for the safety assessment 6-month after vaccination, due to voluntary withdrawal from the study or lost-to-follow-up.

Immunogenicity population:
Thirty-three participants (Menactra n=15, Menomune® n= 18) were excluded from the per-protocol population due to ineligibility (e.g. receipt of a non-study vaccine before study enrollment or during the study period, antibiotic use within 72 hours prior to enrollment) or visits outside the scheduled interval. Sera for an additional two Menactra participants were not available in sufficient quantities for the primary immunogenicity analysis. The per protocol population for immunogenicity thus included 425 Menactra and 423 Menomune® participants.

Demographic characteristics: The distribution of participants, based on age, gender, race and ethnicity, was similar among the two vaccine groups. The study population enrolled was predominately Caucasian (95.2%), but also included African American (3.3%), Hispanic (0.3%), Asian populations (0.2%) and individuals with mixed racial background (0.9%).

7.1.1.4.2 Immunogenicity

Serum bactericidal antibody:
For all serogroups, the percentage of participants with a ≥four-fold increase in SBA-BR antibody titer was 80% or greater in both vaccine groups (MTA-02 Table 1).

MTA-02 Table 1: Number and Percentage of Participants 11-18 Years Old Achieving a ≥ Four-fold Increase in SBA-BR Antibody Titer, with 95%CI

Serogroup	Menomune®			Menactra		
	N= 423			N= 423		
	n*	%†	95% CI§	n*	%†	95% CI§
A	391	92.4%	89.5, 94.8	392	92.7%	89.8, 95.0
C	375	88.7%	85.2, 91.5	388	91.7%	88.7, 94.2
Y	339	80.1%	76.0, 83.8	346	81.8%	77.8, 85.4
W-135	403	95.3%	92.8, 97.1	409	96.7%	94.5, 98.2

*n: number of participants with ≥ 4-fold rise from baseline SBA-BR titer. N: total number of participants with valid serology data.
† %: percentage of participants with a ≥4-fold rise in SBA-BR titer post-vaccination compared with baseline.
§ CI: Confidence interval.

The upper limit of the one-sided 95% confidence interval (CI) for the difference in the two proportions was less than 0.1, for each serogroup (MTA-02 Table 2). The primary hypothesis was also achieved according to current CBER preferences for testing non-inferiority immunogenicity hypotheses, which uses the upper limit of the 2-sided 95% CI.

MTA-02 Table 2: Primary Hypothesis Testing
Proportion of Participants 11-18 Years Old with a ≥Four-fold Increase in SBA-BR Antibody Titer

Serogroup	Menomune® N=422 $p_{Menomune®}$†	Menactra N=423 $p_{Menactra}$‡	Difference ($p_{Menomune®} - p_{Menactra}$)	Upper Limit of the 1-sided 95% CI of the Difference§	Upper Limit of the 2-sided 95% CI of the Difference§
A	0.924	0.926	-0.002	0.027	0.033
C	0.886	0.917	-0.031	0.003	0.009
Y	0.801	0.818	-0.017	0.028	0.036
W-135	0.952	0.966	-0.014	0.008	0.013

† $p_{Menomune®}$: proportion of Menomune® participants with a ≥4-fold rise in SBA-BR titer post-vaccination compared with baseline.
‡ $p_{Menactra}$: proportion of Menactra participants with a ≥ 4-fold rise in SBA-BR titer post-vaccination compared with baseline.
§ CI: Confidence interval.

Seroconversion rate was defined as the proportion of participants with SBA-BR antibody titer less than 1:8 pre-vaccination, who subsequently achieved a four-fold or greater increase in SBA-BR antibody titer 28 days following vaccination. All participants with serogroup A SBA-BR antibody less than 1:8 pre-vaccination, in both groups, achieved seroconversion. For serogroup C, seroconversion was observed in 98.7% [153/155] of Menactra recipients and 99.3% [151/152] of Menomune® recipients. For the remaining serogroups, of those participants who received Menactra, 98.4% [60/61] and 98.2% [161/164] responded with a ≥4-fold antibody rise to serogroups Y and W135, respectively, compared with 100% [47/47] and 93.3% [138/139] of individuals who received Menomune® (Table not shown).

Serogroup-specific IgG and IgM antibody:
Serogroup-specific IgG and IgM geometric mean antibody concentrations, measured by ELISA, were assessed in a subset of 161 participants [Menactra n=82, Menomune® n=79] (MTA-02 Tables 3 and 4). Menomune® elicited higher IgG response post-vaccination to all serogroups, except for serogroup A. Comparison of IgG results and SBA-BR antibody titer for each serogroup showed a general trend, but not a direct correlation, between the two immunogenicity parameters. The IgM response post-vaccination was higher following Menactra vaccination for serogroup A, and similar to Menomune® for the remaining serogroups.

MTA-02 Table 3: Comparison of ELISA IgG Geometric Mean Concentration, and SBA-BR Geometric Mean Titer Post-vaccination, For Each Serogroup

Serogroup	Vaccine Group	Post-vaccination results			
		IgG (µg/mL)	95% CI	SBA-BR GMT	95% CI
A	Menomune®	11.6	8.8, 15.3	3245.7	2910.0, 3620.1
	Menactra	18.1	13.6, 24.1	5483.2	4920.1, 6110.7
C	Menomune®	8.1	5.4, 12.2	1638.9	1405.6, 1910.9
	Menactra	5.5	3.9, 8.0	1924.4	1662.1, 2228.0
Y	Menomune®	9.2	6.6, 12.8	1228.3	1088.2, 1386.4
	Menactra	4.4	2.7, 7.1	1322.3	1161.9, 1504.8
W-135	Menomune®	4.9	3.5, 7.0	1545.0	1383.6, 1725.2
	Menactra	3.0	2.0, 4.3	1407.2	1232.8, 1607.3

Note: The total number of participants with valid serology data for an analysis of serogroup-specific IgG was 161 [Menactra n=82, Menomune n=79], and 846 [Menactra n=423, Menomune® n=423] for SBA-BR GMT.

MTA-02 Table 4: ELISA IgM Geometric Mean Concentrations Post-vaccination, For Each Serogroup			
Serogroup	**Vaccine Group**	**IgM (µg/mL)**	**95% CI**
A	[redacted]	12.0	9.7, 14.9
	Menactra	17.8	14.7, 21.6
C	[redacted]	1.7	1.4, 2.1
	Menactra	1.6	1.2, 2.0
Y	[redacted]	3.5	2.9, 4.2
	Menactra	3.5	2.8, 4.3
W-135	[redacted]	1.7	1.4, 2.0
	Menactra	1.9	1.6, 2.3

7.1.1.4.3 Safety

Overall safety profile: Except for local reactions, the proportion of participants experiencing an adverse event was similar among the two vaccine groups.

MTA-02 Table 5: Overall Participant Safety Profile				
Type of AE	Menactra		[redacted]	
	n/N*	%†	n/N*	%†
Immediate reactions (within 30 minutes)	2/440	0.5	0/441	0
Solicited local reactions (Days 0-7)	317/438	72.4	153/441	34.7
95% Confidence Interval		67.9, 76.5		30.3, 39.3
Solicited systemic reactions (Days 0-7)	251/439	57.2	229/441	51.9
95% Confidence Interval		52.4, 61.9		47.2, 56.7
Unsolicited adverse events (Days 0-28)	165/440	37.5	169/440	38.4
Unsolicited significant adverse events (Day 29-Month 6)	26/436	6.0	18/435	4.1
All serious adverse events (Day 0-Month 6)	5/440	1.1	1/441	0.2

*n: number of participants reporting at least one event in this category.
†%: n/N expressed as a percentage.

Immediate reactions: Two Menactra recipients experienced syncope.

Local reactions:
The occurrence of any injection site reaction was reported by 72.4% and 34.7% of Menactra and Menomune® recipients, respectively. Of these reactions, Menactra participants reported mild pain (52.1% vs. 26.3%), induration (16.7% vs. 7.3%) and swelling (11.2 vs. 4.8%) more frequently compared with Menomune® participants. These reactions occurred mainly within the first three days after vaccination, and the 95% confidence intervals for these adverse event rates were not overlapping. Moderate pain (16.7% vs. 3.9%), induration (3.0% vs. 0.5%) and swelling (2.5% vs. 0.7%) were also more frequent among individuals receiving Menactra. Eight severe local events occurred in 5 Menactra participants. Three Menactra participants experienced severe swelling and induration, which were both larger than 2 inches in diameter; the total duration of each symptom ranged from 1-8 days. The remaining two Menactra participants developed severe localized pain and redness, respectively. None of the Menomune® participants reported severe reactions.

MTA-02 Table 6: Local adverse reactions (Days 0-7)

Reaction	Severity	Menactra N=438			Menomune® N=441		
		n*	%†	95% CI	n*	%†	95% CI
Redness							
	Any	53	12.1	9.2, 15.5	28	6.3	4.3, 9.0
< 1 inch	**Mild**	45	10.3	7.6, 13.5	27	6.1	4.1, 8.8
1 – 2 inches	**Moderate**	7	1.6	0.6, 3.3	1	0.2	0.0, 1.3
> 2 inches	**Severe**	1	0.2	0.0, 1.3	0	0.0	0.0, 0.8
Swelling							
	Any	63	14.4	11.2, 18.0	24	5.4	3.5, 8.0
< 1 inch	**Mild**	49	11.2	8.4, 14.5	21	4.8	3.0, 7.2
1 – 2 inches	**Moderate**	11	2.5	1.3, 4.4	3	0.7	0.1, 2.0
> 2 inches	**Severe**	3	0.7	0.1, 2.0	0	0.0	0.0, 0.8
Induration							
	Any	89	20.3	16.6, 24.4	34	7.7	5.4, 10.6
< 1 inch	**Mild**	73	16.7	13.3, 20.5	32	7.3	5.0, 10.1
1 – 2 inches	**Moderate**	13	3.0	1.6, 5.0	2	0.5	0.1, 1.6
> 2 inches	**Severe**	3	0.7	0.1, 2.0	0	0.0	0.0, 0.8
Pain							
	Any	302	68.9	64.4, 73.3	133	30.2	25.9, 34.7
	Mild	228	52.1	47.3, 56.8	116	26.3	22.3, 30.7
	Moderate	73	16.7	13.3, 20.5	17	3.9	2.3, 6.1
	Severe	1	0.2	0.0, 1.3	0	0.0	0.0, 0.8

*n: number of participants reporting at least one event in this category. Two Menactra participants did not provide any local reaction information. Percentages are based on the total number of participants who did submit safety information at each time point.

†%: n/N expressed as a percentage.

Pain: 0=none, 1= (mild) sx present, but arm movement not affected, 2= (moderate) limits usual arm movement, 3= (severe) disabling

Systemic reactions:

In both groups, headache and fatigue were most frequent. The proportion of participants with any headache was 44.9% in the Menactra group, and 39.5% and Menomune® group. Of the recipients who reported headache, 27.3% and 28.6% of Menactra and Menomune® recipients, respectively, reported this symptom as mild. In addition, 15.9% and 9.1% of participants receiving Menactra and Menomune®, respectively, reported moderate headache. Fatigue occurred in 28.2% and 23.6% of participants receiving Menactra and Menomune®, respectively; approximately 70% of these participants reported mild fatigue.

Excluding rash, 18 solicited severe systemic adverse events occurred in 10 Menactra participants, and 16 events in 11 Menomune® participants. In the Menactra group, five of the 10 participants reported two or more severe systemic reactions, of which one symptom was fatigue. Two participants reported severe headache, with fatigue and anorexia. One Menactra participant reported grade 3 fever (T104.1°C) in association with severe headache and fatigue. In the Menomune® group, 4 of 11 participants reported two or more severe systemic reactions. Of the Menomune® participants with multiple severe reactions, one participant reported severe headache, fatigue and diarrhea. The remaining three Menomune® participants experienced severe headache/ fatigue, severe fatigue/ anorexia, and severe anorexia/ vomiting, respectively. No association between severe systemic reactions and a baseline SBA-BR antibody titer greater than or equal to 1024 was observed.

Rash, occurring within 7 days after vaccination, was reported by seven participants in each group. One participant in each group reported localized rash, located either at or near the injection site. For the remaining participants, rashes described were non-specific, located more often on the extremities than on

the trunk, and lasted a median of two days (range: 1 day to 2 months). A rash reported as hives occurred in one Menactra participant. This study participant developed shortness of breath, which started on the day of vaccination, and responded to albuterol, and gradually improved over 4 days. Hives was reported five days after vaccination, and lasted one day.

MTA-02 Table 7: Systemic adverse reactions (Days 0-7)

Reaction	Severity	Menactra N= 439			Menomune® N= 441		
		n*	%†	95% CI	n*	%†	95% CI
Fever							
	Any	15	3.4	1.9, 5.6	11	2.5	1.3, 4.4
38.0°C-38.9°C	**Mild**	12	2.7	1.4, 4.7	10	2.3	1.1, 4.1
39.0°C-39.9°C	**Moderate**	2	0.5	0.1, 1.6	1	0.2	0.0, 1.3
≥ 40.0°C	**Severe**	1	0.2	0.0, 1.3	0	0.0	0.0, 0.8
Headache							
	Any	197	44.9	40.2, 49.7	174	39.5	34.9, 44.2
	Mild	120	27.3	23.2, 31.8	126	28.6	24.4, 33.0
	Moderate	70	15.9	12.6, 19.7	40	9.1	6.6, 12.1
	Severe	7	1.6	0.6, 3.3	8	1.8	0.8, 3.5
Fatigue							
	Any	124	28.2	24.1, 32.7	104	23.6	19.7, 27.8
	Mild	86	19.6	16.0, 23.6	79	17.9	14.4, 21.8
	Moderate	33	7.5	5.2, 10.4	22	5.0	3.2, 7.5
	Severe	5	1.1	0.4, 2.6	3	0.7	0.1, 2.0
Anorexia							
	Any	54	12.3	9.4, 15.7	54	12.2	9.3, 15.7
Skips 1 meal	**Mild**	40	9.1	6.6, 12.2	39	8.8	6.4, 11.9
Skips 2 meals	**Moderate**	10	2.3	1.1, 4.1	12	2.7	1.4, 4.7
Skips ≥ 3 meals	**Severe**	4	0.9	0.2, 2.3	3	0.7	0.1, 2.0
Vomiting							
	Any	10	2.3	1.1, 4.1	9	2.0	0.9, 3.8
1 episode	**Mild**	7	1.6	0.6, 3.3	2	0.5	0.1, 1.6
2 episodes	**Moderate**	2	0.5	0.1, 1.6	6	1.4	0.5, 2.9
≥3 episodes	**Severe**	1	0.2	0.0, 1.3	1	0.2	0.0, 1.3
Diarrhea							
	Any	48	10.9	8.2, 14.2	62	14.1	11.0, 17.7
1-2 episodes	**Mild**	42	9.6	7.0, 12.7	52	11.8	8.9, 15.2
3-4 episodes	**Moderate**	6	1.4	0.5, 3.0	9	2.0	0.9, 3.8
≥ 5 episodes	**Severe**	0	0.0	0.0, 0.8	1	0.2	0.0, 1.3
Rash							
Any rash	**Days 0-7**	7	1.6	0.6, 3.3	7	1.6	0.6, 3.2

*n: number of participants reporting at least one event in this category. One Menactra participant did not provide any systemic reaction information. Percentages are based on the total number of participants who did submit safety information at each time point.

†%: n/N expressed as a percentage.

Headache, fatigue: 0= none, 1= aware, easily tolerated, 2= interferes with usual activities, 3= disabling

Serious adverse events:

Seven adverse events were reported in six individuals. Five adolescents received Menactra and 1 adolescent received Menomune®. The Menactra participants were hospitalized either for management of a pre-existing condition (deviated septum, torn lateral meniscus), or, an acute condition occurring more than 30 days post-vaccination (pyleonephritis/dehydration, testicular torsion, acetaminophen overdose). One Menomune participant experienced recurrence of supraventricular tachycardia 45 days after

vaccination. All individuals recovered without sequelae. No deaths occurred among participants in the study.

7.1.1.5 Reviewer summary and conclusions for study MTA-02

Study MTA-02 was a trial to evaluate the safety and immunogenicity of Menactra in 11-18 year old participants, compared to Menomune®. The immunogenicity data from this study served as the primary basis for demonstrating non-inferiority to Menomune® in this age group. Safety comparisons, as a secondary objective, were also included.

Immunogenicity: The primary hypothesis, which was to demonstrate that 28-days after vaccination Menactra was non-inferior to Menomune®, was achieved. The primary outcome measure was the proportion of participants with a ≥4-fold increase in serum bactericidal antibody titer, measured with an assay using baby rabbit complement (SBA-BR). The upper limit of the one-sided 95% confidence interval for the difference of the two proportions was not greater than 0.1, for each serogroup. Subsequent to the conduct of study MTA-02, CBER preferences for using a two-sided 95% CI in non-inferiority hypothesis testing evolved to be consistent with the FDA Center for Drugs, and the European Union. The upper limit of the difference in two proportions, using a two-sided 95% CI, was 0.033, 0.010, 0.037, and 0.013 for serogroups A, C, Y and W135, respectively. The primary immunogenicity hypothesis was thus achieved, even by the more stringent of the two statistical criteria.

A baseline SBA-BR antibody titer ≥1:8 to serogroups C and W135 was detected in more than 60% of participants in both vaccine groups. Pre-existing SBA-BR titer ≥1:8 to serogroups A and Y were reported in >80% and >85% of all participants, respectively. Participants in both vaccine groups, with an undetectable SBA-BR antibody titer (<1:8) to serogroup A pre-vaccination, all achieved a four-fold or greater increase in SBA-BR antibody titer 28 days following vaccination. For serogroup C, seroconversion occurred in 98.7% of Menactra and 99.3% of Menomune® recipients, respectively. In addition, of those participants who received Menomune®, 98.4% and 98.2% responded with a ≥4-fold antibody rise to serogroups Y and W135, respectively, compared with 100% and 99.3% of individuals who received Menomune®.

Comparison of IgG results, measured by ELISA, and bactericidal antibody titer for each serogroup showed a general trend, but not a strong correlation, between the two immunogenicity parameters. Measurement of total IgG antibody levels likely reflected detection of low and high avidity antibody, of which high avidity antibody more closely mimics functional antibody response.[14]

Safety: Local reactions were two times more frequent among adolescents receiving a single dose of Menactra, compared with Menomune® participants. The proportion of participants reporting any local reaction was 72.4% and 34.7%, respectively. The 95% CI for each local adverse event were not overlapping between the two vaccine groups. Moderate reactions were also more common among individuals receiving Menactra, particularly moderate pain, which was approximately four times more common in the first 3 days post-vaccination. Eight severe local events occurred in 5 Menactra participants, and none were reported in Menomune® participants.

Headache was most frequent, and occurred in 44.9% and 39.5% of participants in the Menactra and Menomune® groups, respectively. Fatigue was also common, and experienced by 28.2% and 23.6% of participants who received Menactra and Menomune®, respectively. For both symptoms, the majority of reported reactions were mild. Excluding rash, 18 solicited severe systemic adverse events occurred in 10 Menactra participants, and 16 events in 11 Menomune® participants. There was no association between severe systemic reactions and a baseline SBA-BR antibody titer greater than or equal to 1024. Assessments of chills, arthralgia, arthritis and additional rash characteristics (e.g. color, blanching/not blanching, raised/smooth) were not included in this study. Increased frequency of local and systemic

reactions experienced by Menactra recipients could be attributed to the diphtheria toxoid amount in Menactra. The impact of pre-existing antibody to diphtheria is unclear, as a comparison between increased frequency of reactions and elevated pre-vaccination antibody levels to diphtheria toxoid was not evaluated in this study.

Seven serious adverse events were reported in five Menactra participants and one Menomune® participant. Due to the nature and the timing of the event, these adverse events are unlikely to be related to vaccination. There was no apparent increase in the frequency of new onset bronchial asthma, diabetes mellitus, or autoimmune disease during the six-month safety follow-up.

7.1.2 Study MTA-04: A Comparative Trial of the Safety of One Dose of an Experimental Tetravalent (A, C, Y, and W135) Meningococcal Diphtheria Conjugate Vaccine Versus Menomune® A/C/Y/W-135 in Healthy Children in the U.S. Aged 11-18 Years

7.1.2.1 Objectives

- Primary objective:
  - ✓ To describe the safety profile after a single dose of Menactra
  - ✓ To compare the relative frequency of a solicited systemic reaction reported as severe among Menactra and Menomune® recipients

7.1.2.2 Design

The study was a randomized, modified double blind, multi-center, active-controlled trial. Since the routes of administration for the study vaccine differed from the control vaccine, study personnel who administered the vaccine differed from the personnel collecting the safety data. Enrollment was stratified into two age groups (11-14 years, 15-18 years) to ensure adequate representation of participants in each age group. Participants were randomized in a 2.5: 1 (Menactra: Menomune®) ratio.

Study Period: April 16, 2001 to April 10, 2002

7.1.2.3 Protocol

7.1.2.3.1 Population

The study was conducted at thirty-two study centers in the United States.

Inclusion criteria:

- Healthy
- Age ≥11 years and <19 years old at the time of vaccination
- Received a 4th injection of a DTP-containing vaccine, but not within 28 days of enrollment
- Informed assent or parental consent obtained

Exclusion criteria:

- Serious chronic disease (i.e. cardiac, renal, neurologic, metabolic, rheumatologic etc.)
- Known or suspected impairment immunologic function
- History of documented invasive meningococcal disease or previous meningococcal vaccination
- Receipt of immune globulin or other blood products within the previous 3 months, injected or oral corticosteroids within 6 weeks prior to the administration of the study vaccine
- Administration of a vaccine other than the study vaccine within 28 days of enrollment
- Known or suspected hypersensitivity to any vaccine component
- Enrolled in another clinical trial
- Any condition which, in the opinion of the investigator, would pose a health risk to the participant
- Unable to comply with scheduled visits or study procedures
- For females, a positive or equivocal urine pregnancy test result on the day of vaccination

Reasons for deferring vaccination

- Acute medical illness, with or without fever, within the previous 72 hours. Fever was defined as an oral temp ≥37.5C.

7.1.2.3.2 Vaccine administration

Each group received a single dose of vaccine. Menactra was administered intramuscularly, and the control vaccine, Menomune®, given subcutaneously.

7.1.2.3.3 Endpoints

Primary Endpoint:
The proportion of participants with a least one solicited systemic reaction reported as severe during the 7-day period following vaccination.

7.1.2.3.4 Surveillance

Monitored parameters:
Safety: Study participants were monitored for immediate reactions 30 minutes post-vaccination, and for local and systemic reactogenicity during the 7 days following vaccination. Pre-specified adverse events included localized reactions (erythema, swelling, induration, pain) and systemic symptoms (fever measured by oral temperature, headache, fatigue, chills, arthralgia, anorexia, vomiting, diarrhea, seizures, malaise and rash). These events were recorded on a diary card, and also collected by study personnel through telephone interview eight days after vaccination. If rash was reported, the investigator was prompted to record additional details on a separate case report form. Other non-serious, unexpected adverse events were obtained by telephone interview eight and twenty-eight days after vaccination.

Serious adverse events were reported and recorded during the 6-month study period following vaccination. A serious adverse event was defined as any untoward medical occurrence resulting in death, life-threatening experience, inpatient hospitalization, prolonged existing hospitalization, persistent or significant disability/incapacity, or a congenital anomaly/birth defect. In addition to these events, visits to an emergency room, or unexpected visits to an office physician were collected via scripted telephone interview.

7.1.2.3.5 Statistical plan

Primary Hypothesis:
To demonstrate that Menactra is non-inferior to Menomune® in the proportion of participants with a least one solicited systemic reaction reported as severe during the 7-day period following vaccination.

This hypothesis would be supported by the data if the upper limit of the two sided 90% CI of $p_{Menactra}$ / $p_{Menomune®}$ is less than 3, where p represents the proportion of participants with at least one severe solicited systemic reaction in the Menomune® and Menactra groups, respectively. Planned enrollment of 3178 participants (Menactra n=2222, Menomune® n=956), with resultant 2860 evaluable study subjects (Menactra n=2000, Menomune® n=860) provided 80% power to achieve the primary hypothesis. Primary hypothesis testing was conducted at the 0.05 significance level. The sponsor also included an analysis according to current CBER recommendations, which is based on the upper limit of the 2-sided 95% CI.

Since the nature and severity of a rash were difficult to categorize for the vaccine recipient, all rashes occurring during the first 7 days after vaccination were designated by the sponsor as a severe solicited systemic reaction, in an effort to prompt the investigator to describe additional rash characteristics.

Analyses were based upon the total study population, even though enrollment was stratified by age. The intent-to-treat population was used for all analyses.

Per-protocol population for safety:
Eligible participants who received the vaccine according to the treatment assignment were included in the per-protocol population. Although this population was defined, all analyses were performed on the intent-to-treat population.

Intent-to-treat population for safety:
The intent-to-treat population consisted of all participants who received one dose of vaccine and for whom safety information was available. Analyses were performed according to the vaccine received.

7.1.2.4 Results

7.1.2.4.1 Population

A total of 3242 (Menactra n=2270, Menomune® n= 972) adolescents were enrolled, and 3211 (Menactra n= 2250, Menomune® n=961) individuals completed the study.

Safety population:
The intent-to-treat population for safety included 3242 participants (Menactra n=2270, Menomune® n= 972). Thirty-one individuals (Menactra n= 20, Menomune® n=11) did not complete the safety assessment 6-months after vaccination, due to voluntary withdrawal from the study (e.g. moved out of the study area), lost-to-follow-up or non-compliance with study procedures. One Menomune recipient received diluent, but no active component. Four additional participants, two in each group, were randomized but did not receive the assigned vaccine.

Demographic characteristics: The distribution of participants, based on age, gender, race and ethnicity, was similar among the two vaccine groups. The study population enrolled was predominately Caucasian (89.7%), but also included African American (5.4%), Hispanic (2.9%), Asian populations (1.1%) and individuals with mixed racial background (0.9%).

7.1.2.4.2 Safety

Overall safety profile: Except for local reactions, the proportion of participants experiencing an adverse event was not statistically significant between the two vaccine groups.

MTA-04 Table 1: Overall Participant Safety Profile

Type of AE	Menactra		Menomune®	
	n/N*	%†	n/N*	%†
Immediate reactions (within 30 minutes)	8/2270	0.4	3/972	0.3
Solicited local reactions (Days 0-7)	1420/2264	62.7	310/970	32.0
95% Confidence Interval		60.69, 64.72		29.03, 35.00
Solicited systemic reactions (Days 0-7)	1247/2265	55.1	472/970	48.7
95% Confidence Interval		52.98, 57.12		45.47, 51.86
Unsolicited adverse events (Days 0-28)	601/2264	26.5	228/971	23.5
Unsolicited significant adverse events (Day 29- Month 6)	169/2251	7.5	69/962	7.2
All serious adverse events (Day 0-Month 6)	22/2270	1.0	6/972	0.6

*n: number of participants reporting at least one event in this category.
†%: n/N expressed as a percentage.

Immediate reactions: Eight individuals in the Menactra group experienced a reaction within 30 minutes after vaccination. Four participants developed dizziness, with associated hypotension, bradycardia, nausea/vomiting or diaphoresis. The four remaining participants reported syncope, chills with diaphoresis, chest tightness, and moderate injection site reaction, respectively. Three Menomune® participants reported separate symptoms (dizziness, diaphoresis, and mild injection site reaction).

Local reactions:

The occurrence of any injection site reaction was reported by 62.7% [1420/2264] and 32.0% [310/970] of Menactra and Menomune® recipients, respectively. For all solicited local reactions, a mild reaction was reported 2-3 times more frequently by Menactra participants, compared with Menomune® participants; the 95% confidence intervals for these adverse event rates were not overlapping. Mild reactions occurred mainly within the first three days after vaccination, except for localized pain, which was commonly reported throughout the first 7 days following vaccination. Moderate pain (12.8% vs. 2.6%), induration (2.5% vs. 0.5%) and swelling (1.9% vs. 0.3%) also occurred more frequently among individuals receiving Menactra. Thirty-seven severe local reactions occurred in 26 Menactra participants, and none were reported in Menomune® participants. The median duration of local reactions for these participants was 4 days (range 1-13 days). Eight Menactra individuals experienced two or more severe adverse events. All of the eight individuals reported severe swelling, induration, or a combination of both symptoms. Of the remaining 18 individuals, who experienced a single severe local reaction, redness occurred in 9 participants.

MTA-04 Table 2: Local adverse reactions (Days 0-7)

		Menactra			Menomune®		
		N= 2264			N= 970		
Reaction	**Severity**	**n***	**%†**	**95% CI**	**n***	**%†**	**95% CI**
Redness							
	Any	247	10.9	9.65, 12.27	55	5.7	4.30, 7.32
< 1 inch	**Mild**	197	8.7	7.57, 9.94	51	5.3	3.94, 6.86
1 – 2 inches	**Moderate**	37	1.6	1.15, 2.25	4	0.4	0.11, 1.05
> 2 inches	**Severe**	13	0.6	0.31, 0.98	0	0.0	0.00, 0.31
Swelling							
	Any	245	10.8	9.57, 12.17	35	3.6	2.53, 4.98
< 1 inch	**Mild**	191	8.4	7.32, 9.66	32	3.3	2.27, 4.63
1 – 2 inches	**Moderate**	43	1.9	1.38, 2.55	3	0.3	0.06, 0.90
> 2 inches	**Severe**	11	0.5	0.24, 0.87	0	0.0	0.00, 0.31
Induration							
	Any	355	15.7	14.21, 17.24	50	5.2	3.85, 6.74
< 1 inch	**Mild**	292	12.9	11.54, 14.35	45	4.6	3.40, 6.16
1 – 2 inches	**Moderate**	56	2.5	1.87, 3.20	5	0.5	0.17, 1.20
> 2 inches	**Severe**	7	0.3	0.12, 0.64	0	0.0	0.00, 0.31
Pain							
	Any	1340	59.2	57.13, 61.22	278	28.7	25.83, 31.62
	Mild	1045	46.2	44.09, 48.24	253	26.1	23.34, 28.97
	Moderate	289	12.8	11.42, 14.21	25	2.6	1.67, 3.78
	Severe	6	0.3	0.10, 0.58	0	0.0	0.00, 0.31

*n: number of participants reporting at least one event in this category. Six Menactra and 2 Menomune® participants did not provide any data. Percentages are based on the total number of participants who did submit safety information at each time point.

†%: n/N expressed as a percentage.

Pain: 0=none, 1= (mild) sx present, but arm movement not affected, 2= (moderate) limits usual arm movement, 3= (severe) disabling

Systemic reactions:

In both groups, headache was most frequent, and occurred in 35.6% [807/2265] of Menactra participants and 29.3% [284/970] Menomune® participants. Mild headache was reported by 25.0% Menactra participants and 22.4% Menomune® participants, respectively, and occurred mainly within the first three days following vaccination. In addition, 9.6% and 6.5% of participants receiving Menactra and Menomune®, respectively, reported moderate headache. Fatigue was the second most frequent reaction, and experienced by 30.0% and

25.1% of Menactra and Menomune® recipients, respectively; approximately 70% of participants in each group reported mild fatigue. Twenty-six (1.1%) Menactra and two (0.2%) Menomune® participants reported severe fatigue. Mild arthralgias occurred in 13.4% of Menactra participants, and 8.0% of Menomune® participants, respectively. Chills, overall, occurred in 7% [158/2265] of Menactra participants, compared with 3.5% of Menomune® participants; moderate chills occurred in 38 participants (1.7%) and 4 participants (0.4%), respectively. Both arthralgia and chills occurred mainly in the first three days after vaccination.

The rate of severe systemic reactions was 4.3% [97/2265] in the Menactra group and 2.6% [25/970] in the Menomune® group. Excluding rashes, the severe systemic reaction rates were 2.7% and 1.2%, respectively. Of the study population that excluded rash, 108 severe systemic reactions occurred in 61 Menactra participants, and 18 severe reactions in 12 Menomune® participants. Twenty-four of 61 (39%) Menactra participants reported two or more severe systemic reactions. All of the 24 Menactra participants experienced severe fatigue or malaise, and 11of the 24 (46%) participants experienced severe headache. In the Menomune® group, 3 of 12 (25%) participants reported two or more severe systemic reactions. Of the Menomune® participants with multiple severe reactions, one participant reported severe chills in association with severe headache and malaise. The remaining two Menomune® participants experienced anorexia with either severe vomiting or malaise. Although the frequency of participants with ≥2 severe systemic reactions was higher in the Menactra group than the Menomune® group, the difference was not statistically significant. One Menomune® participant reported grade 3 fever (T103.4°C); elevated temperature began one day after vaccination and lasted 3 days.

Rash, occurring within 7 days after vaccination, was reported by 51 participants [Menactra n=37, Menomune® n=14]. Eleven Menactra and three Menomune® participants, respectively, reported localized rash either at or near the injection site. Lesions appeared mainly within the first two days post-vaccination (range 0-5 days), and were described as red or pink, macular or papular, and primarily non-itchy. The mean duration of the rash was 27 hours (range: 1hr-72hr). For the remaining participants with localized rash, rashes described were non-specific, located more often on the extremities than on the trunk, neck or face, and lasted a median of 2 days (range: 40 minutes to 2 months). Three participants reported generalized rash. One participant in each group described the rash as itchy, blanching; one participant required benedryl. The third participant [Menactra] reported a generalized, non-blanching, red, raised rash that occurred two days post-vaccination, and lasted 4 days.

MTA-04 Table 3: Systemic adverse reactions (Days 0-7)

Reaction	Severity	Menactra N=2265			Menomune® N=970		
		n*	%†	95% CI	n*	%†	95% CI
Fever							
	Any	115	5.1	4.21, 6.06	29	3.0	2.01, 4.27
37.5°C-38.4°C	**Mild**	102.	4.5	3.69, 5.44	25	2.6	1.67, 3.78
38.5°C-39.4°C	**Moderate**	13	0.6	0.31, 0.98	3	0.3	0.06, 0.90
≥ 39.5°C	**Severe**	0	0.0	0.00, 0.13	1	0.1	0.00, 0.57
Headache							
	Any	807	35.6	33.65, 37.64	284	29.3	26.43, 32.25
	Mild	566	25.0	23.22, 26.83	217	22.4	19.78, 25.13
	Moderate	217	9.6	8.40, 10.87	63	6.5	5.03, 8.23
	Severe	24	1.1	0.68, 1.57	4	0.4	0.11, 1.05

Cont. MTA-04 Table 3: Systemic adverse reactions (Days 0-7)

Reaction	Severity	Menactra N= 2365 n*	%	95% CI	Menomune® N= 970 n*	%	95% CI
Fatigue							
	Any	679	30.0	28.10, 31.91	243	25.1	22.35, 27.90
	Mild	484	21.4	19.70, 23.12	181	18.7	16.25, 21.26
	Moderate	169	7.5	6.41, 8.62	60	6.2	4.75, 7.89
	Severe	26	1.1	0.75, 1.68	2	0.2	0.02, 0.74
Malaise							
	Any	496	21.9	20.21, 23.66	163	16.8	14.50, 19.31
	Mild	340	15.0	13.56, 16.55	126	13.0	10.94, 15.27
	Moderate	131	5.8	4.86, 6.83	33	3.4	2.35, 4.74
	Severe	25	1.1	0.72, 1.63	4	0.4	0.11, 1.05
Arthralgia							
	Any	394	17.4	15.85, 19.02	99	10.2	8.37, 12.29
	Mild	304	13.4	12.04, 14.89	78	8.0	6.41, 9.93
	Moderate	82	3.6	2.89, 4.47	20	2.1	1.26, 3.17
	Severe	8	0.4	0.15, 0.69	1	0.1	0.00, 0.57
Chills							
	Any	158	7.0	5.96, 8.10	34	3.5	2.44, 4.86
	Mild	115	5.1	4.21, 6.06	29	3.0	2.01, 4.27
	Moderate	38	1.7	1.19, 2.30	4	0.4	0.11, 1.05
	Severe	5	0.2	0.07, 0.51	1	0.1	0.00, 0.57
Anorexia							
	Any	243	10.7	9.48, 12.08	75	7.7	6.13, 9.60
Skips 1 meal	**Mild**	190	8.4	7.28, 9.61	62	6.4	4.94, 8.12
Skips 2 meals	**Moderate**	46	2.0	1.49, 2.70	11	1.1	0.57, 2.02
Skips ≥ 3 meals	**Severe**	7	0.3	0.12, 0.64	2	0.2	0.02, 0.74
Vomiting							
	Any	44	1.9	1.41, 2.60	14	1.4	0.79, 2.41
1 episode	**Mild**	29	1.3	0.86, 1.83	6	0.6	0.23, 1.34
2 episodes	**Moderate**	9	0.4	0.18, 0.75	5	0.5	0.17, 1.20
≥3 episodes	**Severe**	6	0.3	0.10, 0.58	3	0.3	0.06, 0.90
Diarrhea							
	Any	271	12.0	10.66, 13.37	99	10.2	8.37, 12.29
1-2 episodes	**Mild**	228	10.1	8.86, 11.38	86	8.9	7.15, 10.83
3-4 episodes	**Moderate**	36	1.6	1.12, 2.19	13	1.3	0.72, 2.28
≥ 5 episodes	**Severe**	7	0.3	0.12, 0.64	0	0.0	0.00, 0.31
Seizures (Y/N)							
Yes	**Days 0-7**	0	0.0	0.00, 0.13	0	0.0	0.00, 0.31
Rash							
Any rash	**Days 0-7**	37	1.6	1.15, 2.24	14	1.4	0.79, 2.41

*n: number of participants reporting at least one event in this category. Five Menactra and 2 Menomune® participants did not provide any data. Percentages are based on the total number of participants who did submit safety information at each time point.

†%: n/N expressed as a percentage.

Headache, chills, arthralgia, fatigue, malaise: 0= none, 1= aware, easily tolerated, 2= interferes with usual activities, 3=disabling

MTA-04 Table 4: Rash characteristics				
Rash Description	Menactra		Menomune®	
	n/N*	%†	n/N	%
Number of Participants with at least one Rash	37/2265‡	1.6	14/970	1.4
Local	34/37	91.9	13/14	92.9
General	2/37	5.4	1/14	7.1
Raised	24/37	64.9	8/14	57.1
Smooth	12/37	32.4	6/14	42.9
Itchy	16/37	43.2	5/14	35.7
Not Itchy	20/37	54.1	9/14	64.3
Blanching‡	15/37	40.5	4/14	28.6
Not Blanching	20/37	54.1	10/14	71.4
Color				
Pink	15/37	40.5	4/14	28.6
Red	17/37	45.9	7/14	50
Purple	1/37	2.7	0/14	0
Brown	1/37	2.7	0/14	0
Other	2/37	5.4	3/14	21.4
Duration				
< 1 Hour	1/37	2.7	1/14	7.1
1 to < 24 Hours	12/37	32.4	1/14	7.1
≥ 24 Hours	23/37	62.2	12/14	85.7

*n: number of participants reporting at least one event in this category.
†%: n/N expressed as a percentage.
‡ One Menactra participant did not provide any rash information. Blanching information is missing for a second Menactra participant.

Serious adverse events:
Twenty-eight individuals reported serious adverse events [Menactra n=22, Menomune® n=5]:

- ✓ For seven study participants [Menactra n=5, Menomune® n=2], the event was a newly diagnosed illness that required long-term management of symptoms (juvenile diabetes, Crohn's disease, acute myelogenous leukemia, abdominal adenopathy, depression), or was a result of prolonged treatment for chronic sx (severe esophagitis due to extended NSAID use for a sports-related back injury).
- ✓ Hospitalizations for acute infection (gastroenteritis [*E. coli*, viral], hepatitis B/Epstein Barr virus hepatitis, viral meningitis, pericarditis due to Para influenza type 4), or management of other acute medical conditions (Excedrin overdose, motor vehicle or occupational-related injury, appendicitis, and ruptured ectopic pregnancy with associated anemia) occurred in 10 Menactra participants. All acute infections occurred more than 100 days post-vaccination, and three of five acute medical conditions occurred ≥60 days after vaccination. One study participant developed abdominal pain, nausea and vomiting 11 days following vaccination, which subsequently resulted in a laparoscopic appendectomy. The other study participant sustained open comminuted fractures to the right foot due to an accident 30 days after vaccination. The recovery for both participants was uneventful.
- ✓ The remaining 11 participants were hospitalized for management of a pre-existing condition (recurrent tonsillitis, deviated septum, motor vehicle or recreational-related injury, excess alcohol use, exacerbation of depression/bipolar disorder, and anaphylactic reaction to known allergens). All individuals recovered without sequelae.
- ✓ No deaths occurred among participants in the study.

Primary safety hypothesis testing:

The upper limit of the two-sided 90% confidence interval for the proportion of participants with at least one severe solicited systemic reaction, which included all rashes, in the Menomune® and Menactra groups, respectively, was less than 3-fold. A CBER preference for two-sided 95% confidence intervals evolved subsequent to the planning and conduct of this trial. The primary hypothesis was also achieved according to current CBER requirements for testing non-inferiority safety hypotheses. The upper limit of the two-sided 95% confidence interval for ratio of two proportions was 2.62.

MTA-04 Table 5: Primary Hypothesis Testing
Percentage of Participants 11-18 Years Old With At Least One Severe Solicited Systemic Reaction

Menactra	Menomune®		Upper Limit of the 2-sided 90% CI‡	Upper Limit of the 2-sided 95% CI‡
N= 2265	N= 970			
%†		Ratio $p_{Menactra}$ / $p_{Menomune®}$	of the Ratio	of the Ratio
4.3%	2.6%	1.662	2.42	2.62

N= Total number of participants for whom safety information is available
†%: percentage of participants with at least one severe systemic reaction or rash in the Menactra and Menomune® groups, respectively.
‡CI: Confidence interval.

Note: For analysis purposes, all rashes were counted as severe solicited systemic reactions. Also, for each reaction, each participant is counted no more than once.

7.1.2.5 Reviewer summary and conclusions for study MTA-04

This trial was the pivotal study to evaluate the safety of Menactra in individuals 11-18 years old, compared to Menomune®. The occurrence of any injection site reaction was reported by 62.7% and 32.0% of Menactra and Menomune® recipients, respectively. Menactra participants reported mild reactions 2-3 times more frequently than Menomune® participants. Moderate reactions were also more common among individuals receiving Menactra, particularly moderate pain, which was approximately four times more common in the first 3 days post-vaccination. The 95% confidence intervals for each of these adverse event rates were not overlapping, and were consistent with the adverse event rates observed in MTA-02. Thirty-seven severe local reactions occurred in 26 Menactra participants, and none were reported in Menomune® participants. Eight individuals experienced two or more severe adverse events. All of these individuals reported swelling, induration, or a combination of both symptoms. In both groups, headache and fatigue were most frequent. Both symptoms were mainly mild, and developed within the first three days following vaccination. Mild arthralgia (13.4% vs. 8.0%) was approximately 1.5 times more frequent in the Menactra group compared with participants receiving Menomune®. Chills, overall, occurred twice as frequently (7% vs. 3.5%) in the Menactra group compared with the Menomune® group, with moderate chills reported in 38 participants (1.7%) and 4 participants (0.4%), respectively. Arthralgia and chills both occurred mainly in the first three days after vaccination. In the Menactra group, 4.3% [97/2265] of participants reported a systemic reaction as severe, compared with 2.6% [25/970] in the Menomune® group. Severe malaise and headache were most common in both groups. Grade 3 fever, defined as an oral temperature ≥39.5C, was not a prominent feature in either group. No seizures occurred in either group. Increased frequency of local and systemic reactions in the Menactra group could be attributed to the diphtheria toxoid amount in Menactra.

The primary hypothesis to demonstrate that Menactra is non-inferior to Menomune® in the proportion of participants with at least one solicited systemic reaction reported as severe during the 7-day period following vaccination was achieved by the proposed statistical criteria. The primary hypothesis was also achieved according to current CBER preferences for testing non-inferiority safety hypotheses, in that the upper limit of the two-sided 95% confidence interval for ratio of two proportions was 2.62. When rashes were excluded from the analysis, the percentage of participants with at least one severe systemic adverse event was 2.7% in the Menactra group and 1.2% in the Menomune group. Although a higher percentage of Menactra participants had multiple severe systemic reactions, the difference was not statistically significant.

7.1.3 Study MTA-09: A Comparative Trial of the Safety and Immunogenicity of an Experimental Tetravalent Meningococcal (A, C, Y, and W-135) Diphtheria Conjugate Vaccine, TetraMenD, Compared with Menomune® A/C/Y/W-135 in Healthy Adults in the U.S.

7.1.3.1 Objectives

- Primary objective:
  - ✓ To compare the safety profile for Menactra and Menomune® recipients, as measured by the proportion of participants with at least one solicited systemic reaction reported as severe during the 7-day period following vaccination.
  - ✓ To compare the bactericidal antibody response to serogroups A, C, Y, W135, using baby rabbit complement (SBA-BR), among healthy adults immunized with Menactra with the SBA-BR responses following vaccination with a licensed meningococcal polysaccharide vaccine.

- Other objectives:
  - ✓ To compare the safety profile for Menactra and Menomune® recipients after a single injection.
  - ✓ To describe any relationship between post-vaccination reactogenicity and elevated pre-vaccination SBA-BR titers to each serogroup among recipients receiving either Menactra or Menomune®.
  - ✓ To describe and compare the SBA-BR response to each serogroup pre- and 28 days post-vaccination for Menactra and Menomune® recipients.
  - ✓ To describe and compare the proportion of participants who achieve seroconversion 28 days following a single dose of either Menactra or Menomune®.

7.1.3.2 Design

The study was a randomized, modified double blind, multi-center, active-controlled trial. Since the route of administration for the study vaccine differed from the control vaccine, study personnel who administered the vaccine differed from the personnel collecting the safety data. Enrollment was stratified by two age groups (18-25 years, 26-55 years) to ensure adequate representation of participants in each age group. Participants were randomized in a 1: 1 (Menactra: Menomune®) ratio.

Study Period: October 12, 2001 to July 12, 2002

7.1.3.3 Protocol

7.1.3.3.1 Population

The study was conducted at thirty-three study centers in the United States.

Inclusion criteria:
- Healthy
- Age ≥18 years and <56 years old at the time of vaccination
- Informed consent obtained

Exclusion criteria:
- Serious chronic disease (i.e. cardiac, renal, neurologic, metabolic, rheumatologic etc.)
- Known or suspected impairment immunologic function
- History of documented invasive meningococcal disease or previous meningococcal vaccination
- Receipt of immune globulin or other blood products within the previous 3 months, injected or oral corticosteroids within 6 weeks prior to the administration of the study vaccine
- Administration of a vaccine other than the study vaccine within 28 days of enrollment

- Antibiotic therapy within 72 hours prior to vaccination
- Known or suspected hypersensitivity to any vaccine component
- Enrolled in another clinical trial
- Any condition which, in the opinion of the investigator, would pose a health risk to the participant
- Unable to comply with scheduled visits or study procedures
- For females, a positive or equivocal urine pregnancy test result on the day of vaccination
- Breastfeeding

Reasons for deferring vaccination

- Acute medical illness, with or without fever, within the previous 72 hours. Fever was defined as an oral temp ≥37.5C.

7.1.3.3.2 Vaccine administration

Each group received a single dose of vaccine. Menactra was administered intramuscularly, and the control vaccine, Menomune®, given subcutaneously.

7.1.3.3.3 Endpoints

Primary Endpoints:
Safety: The proportion of participants with a least one solicited systemic reaction reported as severe during the 7-day period following vaccination.

Immunogenicity: The proportion of participants with a ≥4-fold rise in SBA-BR titer for *N. meningitidis* serogroups A, C, Y and W-135.

Secondary endpoint (immunogenicity):
SBA-BR GMT for serogroups A,C,Y,W135 in the Menactra group, compared to corresponding GMTs in the Menomune group.

7.1.3.3.4 Surveillance

Monitored parameters:
Safety: Study participants were monitored for immediate reactions 30 minutes post-vaccination, and for local and systemic reactogenicity during the 7 days following vaccination. Pre-specified adverse events included localized reactions (erythema, swelling, induration, pain) and systemic symptoms (fever measured by oral temperature, headache, fatigue, chills, arthralgia, anorexia, vomiting, diarrhea, seizures, malaise and rash). These events were recorded on a diary card, and also collected by study personnel through telephone interview eight days after vaccination. If rash was reported, the investigator was prompted to record additional details on a separate case report form. Other non-serious, unexpected adverse events were obtained by telephone interview eight and twenty-eight days after vaccination.

Serious adverse events were reported and recorded during the 6-month study period following vaccination. A serious adverse event was defined as any untoward medical occurrence resulting in death, life-threatening experience, inpatient hospitalization, prolonged existing hospitalization, persistent or significant disability/incapacity, or a congenital anomaly/birth defect. In addition to these events, visits to an emergency room, or unexpected visits to an office physician were collected via scripted telephone interview.

Efficacy (Immunogenicity): Serum samples were obtained pre- and 28 days post-vaccination. For all study participants, functional antibody activity to each serogroup, was determined using a serum bactericidal assay. The lower limit of detection for this assay, using baby rabbit complement, is an antibody titer of 8.

7.1.3.3.5 Statistical plan

Primary Hypotheses:
Primary hypothesis# 1 (safety): To demonstrate that Menactra is non-inferior to Menomune® in the proportion of participants with a least one solicited systemic reaction reported as severe during the 7-day period following vaccination.

This hypothesis would be supported by the data if the upper limit of the two-sided 90% CI (one-sided 95% CI) of $p_{Menactra} / p_{Menomune®}$ is less than 3, where p represents the proportion of participants with at least one severe solicited systemic reaction in the Menomune® and Menactra groups, respectively. Planned enrollment of 2455 participants (Menactra n=1333, Menomune® n=1122), with resultant 2210 evaluable study subjects (Menactra n=1200, Menomune® n=1010) provided 80% power to achieve the primary hypothesis. All tests of the primary hypothesis were conducted at the 0.05 significance level. During the course of the trial, CBER requested that the data supporting this hypothesis be based on the upper bound of a two-sided 95% CI, due to changed criteria preferred by CBER for one-sided equivalence trials. The sponsor included an additional analysis according to this criterion.

The intent-to-treat population was used for the primary analysis. Since the nature and severity of a rash were difficult to categorize for the vaccine recipient, all rashes occurring during the first 7 days after vaccination were designated by the sponsor as a severe solicited systemic reaction, in an effort to prompt the investigator to describe additional rash characteristics.

Primary hypothesis# 2 (immunogenicity): To demonstrate that 28-days after vaccination, Menactra is non-inferior to Menomune® by proportion of participants with a ≥4-fold rise in SBA-BR titer for *N. meningitidis* serogroups A, C, Y and W-135.

This hypothesis would be supported by the data if the upper bound of the two-sided 95% CI of $p_{Menomune®} - p_{Menactra}$ is less than 0.10, where p represents the proportion of participants with a ≥4-fold rise in SBA-BR titer as compared to baseline, for each serogroup, respectively. Planned enrollment of 2455 participants, with resultant 2210 evaluable study subjects (Menactra n=1200, Menomune® n=1010) provided 99.9% power, overall, to achieve the primary hypothesis for serogroups A, C, Y and W135. All tests of the primary hypothesis used a type I error of 0.025. The primary analysis was based on data generated from the per-protocol population.

The confidence interval used for primary immunogenicity hypothesis testing was modified during the trial, from a two-sided 90% CI to a two-sided 95% CI, due to changed criteria preferred by CBER for one-sided equivalence trials.

Secondary Hypothesis (immunogenicity): To demonstrate that 28-days after vaccination, the GMT for serogroups A,C,Y,W135 in the Menactra group is non-inferior to corresponding GMTs in the Menomune group. This hypothesis would be supported by the data if the upper limit of the two-sided 95% CI of $GMT_{Menactra} / GMT_{Menomune} < \log_2(2)$ for each serogroup. GMTs are calculated as a log base 2 titer, and adjusted for baseline disparities in pre-existing antibody, using an analysis of covariance with baseline outcome as a covariate. Analyses of the secondary point were performed on both per-protocol and intent-to-treat populations.

Intent-to-treat population for safety:
The intent-to-treat population consisted of all participants who received one dose of vaccine and for whom safety information was available. Analyses were performed according to the vaccine received. The analyses were based upon the total study population, regardless of age stratification.

Per-protocol population for immunogenicity:
The per-protocol population included all eligible participants who received one dose of vaccine according to the treatment assignment, who complied with scheduled visits for blood specimens, and for whom a sufficient quantity of paired sera was available for analysis.

Intent-to-treat population for immunogenicity:
The intent-to-treat population consisted of all enrolled participants who received one dose of vaccine underwent the first blood draw. Analyses were performed according to the vaccine received.

For analysis purposes, if the SBA-BR antibody titer to any serogroup was reported below the limit of detection, the antibody titer assigned was a value equal to the limit of detection. ITT analyses for both the primary and secondary immunogenicity endpoints were considered exploratory. These results were not included in the license application, but anticipated to be submitted as an appendix to the final study report.

7.1.3.4 Results

7.1.3.4.1 Population

A total of 2554 (Menactra n=1384, Menomune® n= 1170) adults were enrolled, and 2400 (Menactra n=1301, Menomune® n= 1099) individuals completed the study.

Safety population:
The intent-to-treat population for safety included 2530 participants (Menactra n=1371, Menomune® n= 1159). One hundred fifty-four participants (Menactra n=83, Menomune® n= 71) were not available for the safety assessment 6 months after vaccination, due to voluntary withdrawal, non-compliance with study procedures, lost-to-follow-up, or other (e.g. no telephone available).

Immunogenicity population:
One hundred fifty-five participants (Menactra n=92, Menomune® n=63) of 301 participants were excluded from the per-protocol population for reasons such as ineligibility (e.g. prior receipt of a meningococcal vaccine, presence of chronic medical conditions, antibiotic use within 72 hours prior to enrollment), non-compliance with study procedures, or visits outside the scheduled interval. Sera for two Menomune® participants were not available in sufficient quantities for the primary immunogenicity analysis. The remaining participants with a protocol violation were considered evaluable for the per-protocol analysis, since the violation related to safety data collection, rather than sera collection or processing. Forty-three participants, for whom Day 8 safety follow-up was either outside the window or not done, were considered evaluable for the per-protocol analysis; of these participants, 81% [35/43] were enrolled at a single study site.

Twelve Menactra participants and 9 Menomune® participants, while not listed for protocol violations, were excluded from the per-protocol population for reasons stated in MTA-09 Table 1. One Menomune® recipient received diluent, but no active component.

MTA-09 Table 1: Participant disposition for immunogenicity analyses		
	Menactra	**Menomune®**
ITT population for immunogenicity	1384 (100.0)	1170 (100.0)
I. Any protocol violation	176 (12.7%)	125 (10.7%)
• Any protocol violation, but participant included in PP pop'n†	84 (6.1%)	62 (5.3%)
Ineligibility criteria	6	2
6m safety f/u outside window	40	35
Day 8 safety f/u outside window	25	18
Documentation	11	7
Other: Participant had hysterectomy, no urine sample collected for pregnancy testing; 6m safety f/u completed by parent rather than the participant	2	0
• Excluded due to protocol violation	92 (6.6%)	63 (5.4%)
II. Participants excluded from the per-protocol (PP) population for immunogenicity	104 (7.5%)	72 (6.2%)
• Participant excluded due to protocol violation	92 (6.6%)	63 (5.4%)
• Not listed as protocol violation, but participant excluded from PP population	12 (0.9%)	9 (0.8%)
Non-compliance	10	6
Visit for blood draw outside window	1	2
Visit, but blood sample not obtained	1	0
Received diluent only	0	1
III. PP population for immunogenicity	1280 (92.5%)	1098 (93.8%)

†Two participants had more than one protocol violation (Participant #946 (Menomune) ineligibility, visit #2 outside window; Participant #1530 (Menactra) urine sample not collected for pregnancy testing (hysterectomy), 6m follow-up outside window. These participants were counted only once according to their first violation.

Demographic characteristics: The distribution of participants, based on age, gender, race and ethnicity, was similar among the two vaccine groups. The study population enrolled was predominately Caucasian (85.0%), but also included African American (5.1%), Hispanic (5.8%), Asian populations (2.7%) and individuals with mixed racial background (1.4%).

7.1.3.4.2 Immunogenicity

Serum bactericidal antibody:

MTA-09 Table 2: Number and Percentage of Participants 18-55 Years Old Achieving a ≥ Four-fold Increase in SBA-BR Antibody Titer, with 95%CI						
Serogroup	**Menomune®**			**Menactra**		
	N= 1070			N= 1280		
	n*	%†	95% CI§	n*	%†	95% CI§
A	929	84.6%	82.3, 86.7	1030	80.5%	78.2, 82.6
C	985	89.7%	87.8, 91.4	1133	88.5%	86.6, 90.2
Y	872	79.4%	76.9, 81.8	941	73.5%	71.0, 75.9
W-135	1036	94.4%	92.8, 95.6	1144	89.4%	87.6, 91.0

*n: number of participants with ≥ 4-fold rise in SBA-BR from baseline. N: total number of participants with valid serology data.
† %: percentage of participants with a ≥4-fold rise in SBA-BR titer post-vaccination, compared with baseline.
§ CI: Confidence interval.