Vaccines and Related Biological Products Advisory Committee

Meeting Date: September 22, 2004

FDA Clinical Briefing Document for

Aventis Pasteur Inc.
Menactra™: Tetravalent Meningococcal Conjugate Vaccine

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CBER/FDA

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1.0 General Information

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

Proposed trade name: Menactra

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.

Sponsor: Aventis Pasteur Inc.

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

Proposed age group: 11-55 years old

Dosing regimen and Route of administration: Single dose, intramuscularly

2.0 Introduction and Background

2.1 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] 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]

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.[2] There have also been increased reports of localized serogroup C outbreaks. Eight outbreaks occurred during a two-year timeframe [1991-1993], compared with 13 outbreaks in the previous decade [1980-1990].[3] Cases of serogroup W135 meningococcal disease were also reported in association with an outbreak among travelers returning from the Hajj, in 2000-2001.[4] 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.[2] 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).[5-7]

2.2 Immune Correlate: Serum Bactericidal Antibody

The presence of bactericidal antibody has been shown to correlate with both natural and vaccine-induced protection against meningococcal disease. The basis for accepting serum bactericidal antibody as an immunologic correlate originated from studies conducted in the 1960's.[8,9] Military recruits with naturally acquired bactericidal antibody were shown to be protected from meningococcal group C disease. The presence of bactericidal antibody was determined using a serum bactericidal assay (SBA) with a human complement (HC) source. A positive result, which indicated the presence of complement mediated anti-meningococcal group C antibody killing, was qualitatively measured at an estimated dilution of 1: 4.

In vitro measurement of bactericidal antibody was indicative of functional activity *in vivo*, and serum bactericidal antibody was hence considered to be a reliable predictor of vaccine effectiveness for serogroups A, C, Y and W135.

2.3 Regulatory background

2.3.1 Use of Immunologic Correlates for Licensure of Meningococcal Vaccines

Demonstration of efficacy, inferred from immunogenicity data, was an approach used as a basis for U.S. licensure of a meningococcal quadrivalent polysaccharide (PS) vaccine, 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, as a basis of vaccine effectiveness, was discussed at a Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting on September 15, 1999,[10] as an approach to support approval of new meningococcal conjugate vaccines. The outcomes of the VRBPAC meeting 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 PS vaccine is licensed, serum bactericidal antibody can be used as a predictor of vaccine efficacy

2.3.2 Basis for Licensure

Proposed licensure of Menactra is based on the following aspects

- ?? Demonstration of efficacy (immunogenicity) compared to Menomune?
- ?? Demonstration of safety compared to Menomune?
- ?? Demonstration of lot consistency

3.0 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	Subjects: Menactra: Menomune? (Ma:Me)			
			Planned		Enrolled	
			N	Ma:Me	N	Ma:Me
Pivotal Studies						
MTA-02 USA	Safety + Immunogenicity	11-18 yrs	812	406: 406	881	440: 441
MTA-04 USA	Safety	11-18 yrs	3178	2222: 956	3242	2270: 972
MTA-09 USA	Safety + Immunogenicity	18-55 yrs	2455	1333: 1122	2554	1384: 1170
MTA-14 USA	Lot consistency	18-55 yrs 26-55 yrs	2039	1599+ 440	2040	1582+ 458
MTA-11 USA	Concomitant Vaccination: Typhim Vi eval.	18-55 yrs	890	Gr A: 445 Gr B: 445	945	Gr A: 469 Gr B: 476
MTA-12 USA	Concomitant Vaccination: Td eval.	11-17 yrs	1024	Gr A: 512 Gr A: 512	1081	Gr A: 509 Gr B: 512
Supplemental Studies- adults						
603-01 USA	Dose escalation, Safety + Immuno	18-55 yrs		30*:0		30*:0
Total 11-55y:			**Planned:**	**N= 10, 428**	**Enrolled:**	**N= 10, 713**
				Menactra: 7504 Menomune: 2924		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, an expanded safety study in healthy U.S. and Chilean children 2-10 years old

3.1 Control vaccine: Menomune® A/C/Y/W135

The active control vaccine implemented in the comparative immunogenicity and safety studies was 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. A single dose was administered subcutaneously.

3.2 Menactra bactericidal antibody results, using baby rabbit and human complement, compared to Menomune® :

Human sera that lack anti-meningococcal antibodies are a difficult source of exogenous complement to locate. In contrast, baby rabbit sera are widely available, and assay results using this complement source are highly reproducible. Serogroup C meningococcal antibody titers, generated from an assay with a rabbit complement source, have been shown to be elevated relative to results using human complement. Consequently, SBA-BR results might overestimate efficacy against group C meningococcus. Less bactericidal antibody data, generated from assays with the two complement sources, are available for serogroups A, Y and W135.

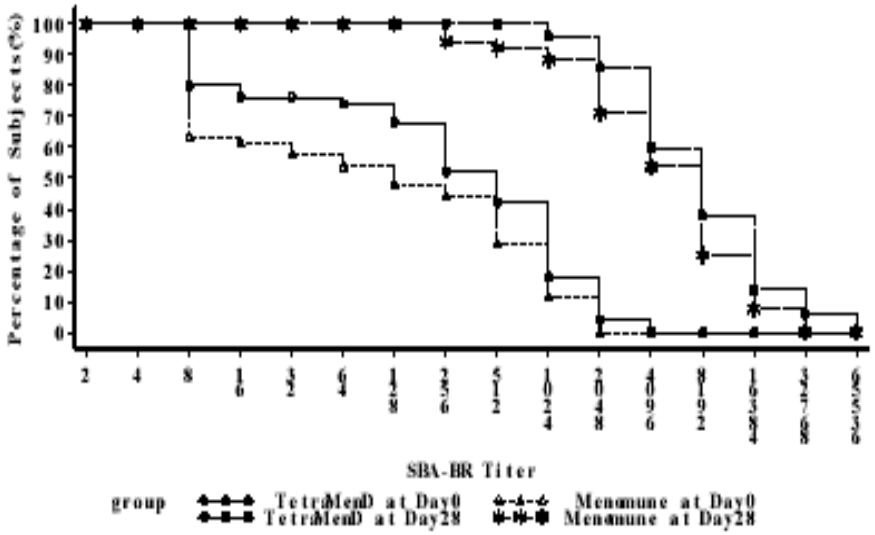
The sponsor was asked to test sera from Menactra and Menomune® participants vaccinated in the same clinical studies, with both a bactericidal assay using baby rabbit complement and an assay using exogeneous human complement. Analyses were based on the participants for whom sufficient sera were available. Pre- and post-vaccination sera were collected from 165 (Menactra n= 84, Menomune®, n=81) non-randomized participants enrolled in study MTA-02 (11-18 years old), and 100 (n= 50 per group) participants in study MTA-09 (18-55 years old). Antibody results for serogroups C, Y and W135 were generated from sera obtained from study MTA-02, and data for serogroups Y and W135, from study MTA-09. Sera from separate subset of 102 MTA-02 participants were used for serogroup A antibody results.

Immune responses were assessed by reverse cumulative distribution curves, seroresponse and seroconversion rates. The seroresponse rate was defined as the proportion of participants with $\geq$ four-fold increase in SBA-BR titer post-vaccination, compared to baseline. 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. For SBA-H results, seroresponse rate was defined as the proportion of participants with SBA-H titer $\geq$ 4 post-vaccination. Seroconversion rate was also defined as the proportion of participants with SBA-H antibody titer less than 1:4 pre-vaccination, who subsequently achieved a titer of $\geq$1: 4, twenty-eight days following vaccination.

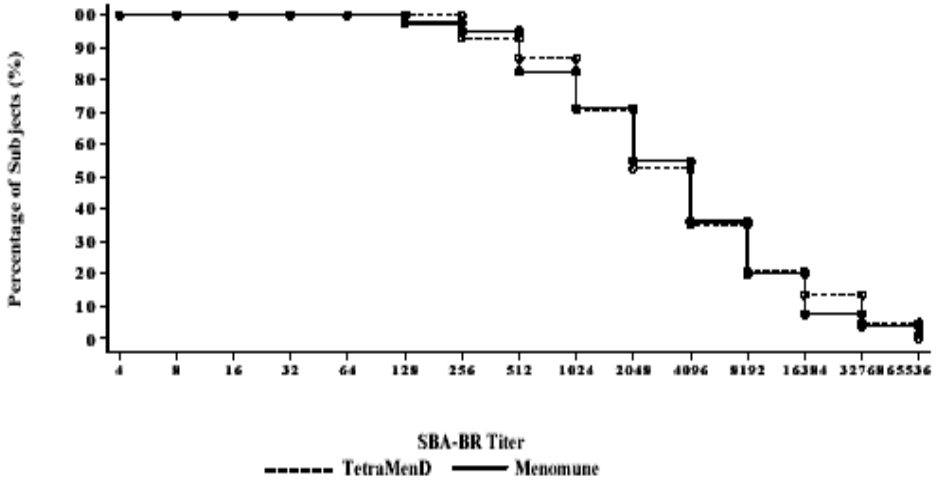
Menactra SBA antibody responses, compared to Menomune, showed general agreement by comparison of reverse cumulative distributions curves, seroresponse and seroconversion rates. The sample size, however, was not large enough to make definite conclusions. Assay sensitivity and specificity were not noticeably different among two populations (adolescents, adults), serogroup (A, C, Y, W135), or vaccine (polysaccharide, conjugate). Misclassification of seroresponders that might occur when SBA results are generated with a rabbit complement source were similarly represented in the two vaccine groups and results were without bias towards Menomune® or Menactra. True susceptible individuals, predicted by a SBA-H titer < 4, however, were not the same susceptible individuals identified by the SBA-BR assay. Thus, the SBA-BR assay has utility as an indicator of vaccine –induced antibody response on a population basis, and is less predictive of individual susceptibility to meningococcal disease.

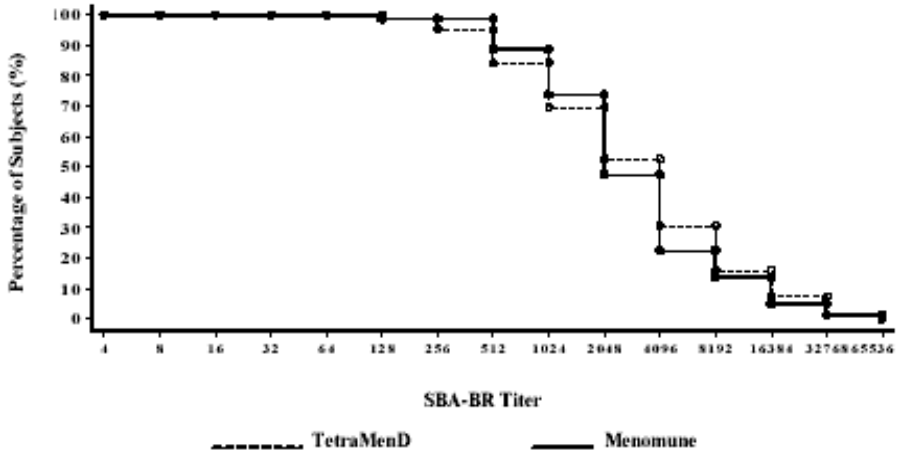
SBA-BR Reverse cumulative distributions curves (11-18 years old)

Serogroup A

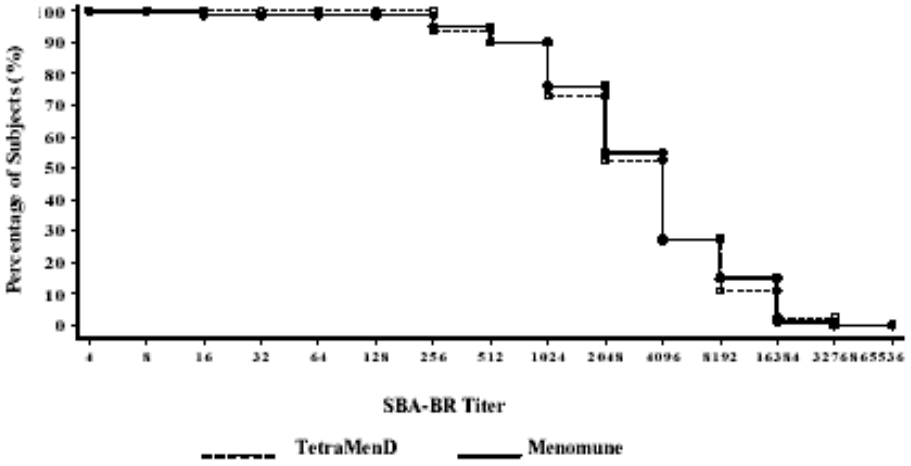


Serogroup C





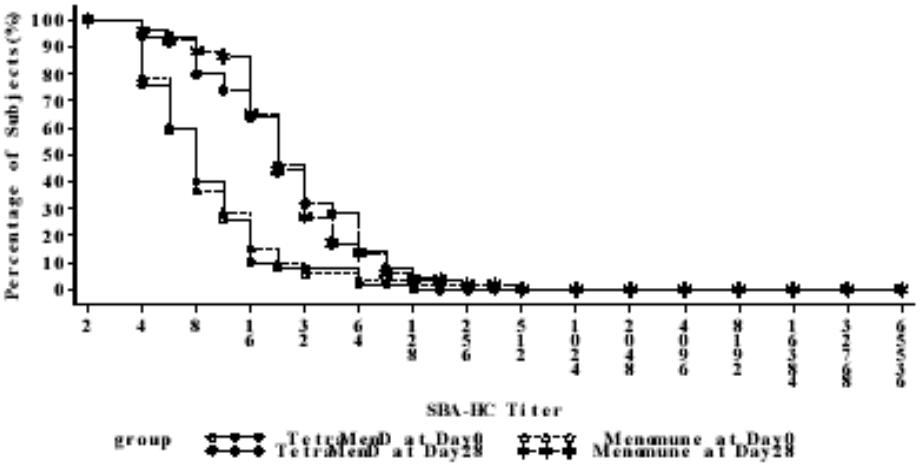
Serogroup Y



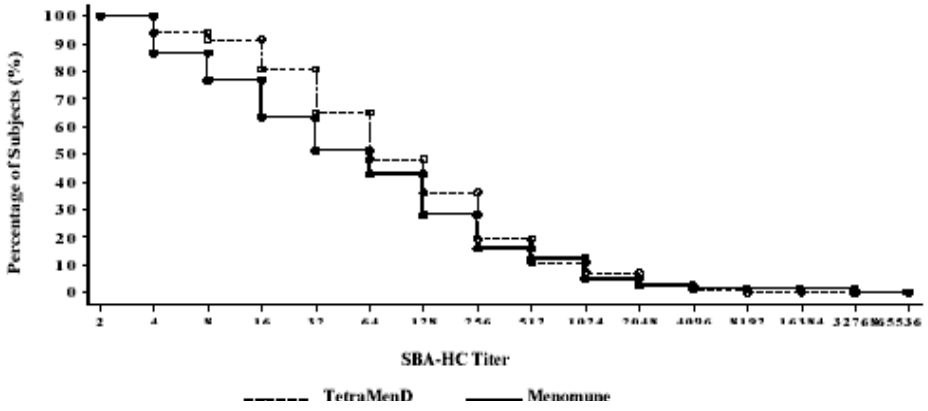
Serogroup W135

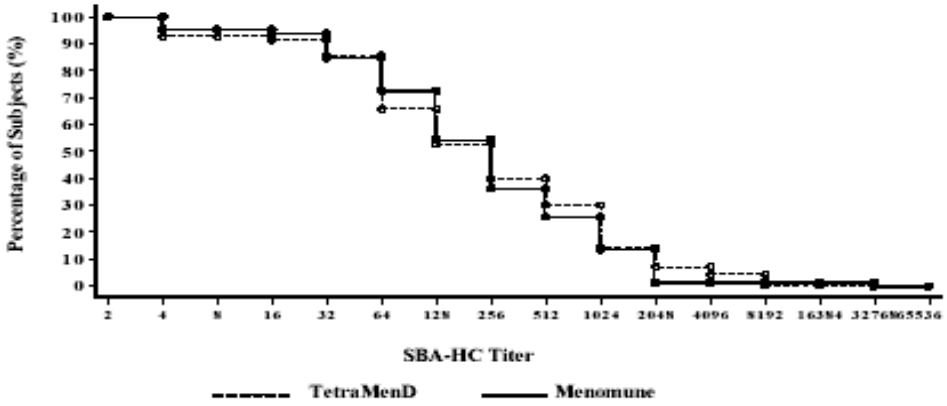
SBA-H Reverse cumulative distributions curves (11-18 years old):

Serogroup A



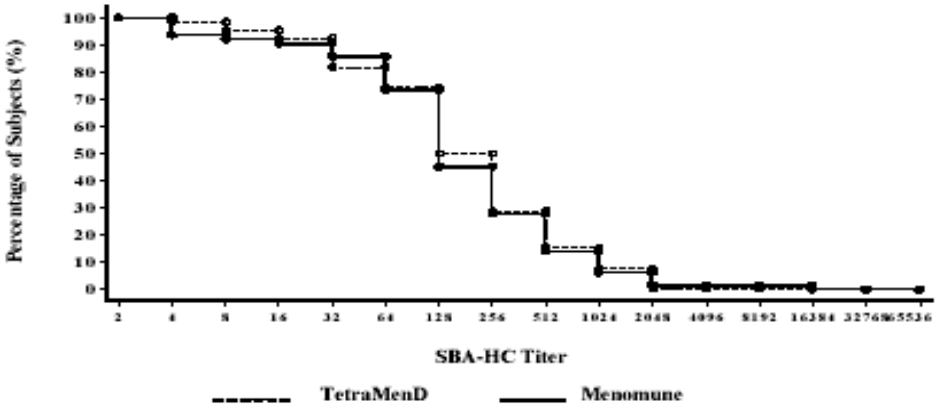
Serogroup C





Serogroup Y

Serogroup W135



11-18 years old:
Seroresponse Rate:
SBA-BR

Serogroup	Menomune (Me)		Menactra (Ma)		Diff (Me-Ma)	95% CI for the Difference
	N	Proportion	N	Proportion		
A	52	0.98	50	0.88	0.1	-0.00, 0.22
C	81	0.9	84	0.89	0.01	-0.09, 0.11
Y	62	0.81	65	0.94	-0.13	-0.26, -0.02
W	58	0.97	61	0.97	0	-0.09, 0.08

SBA-H

Serogroup	Menomune (Me)		Menactra (Ma)		Diff (Me-Ma)	95% CI for the Difference
	N	Proportion	N	Proportion		
A	52	0.96	50	0.94	0.02	-0.08, 0.13
C	81	0.86	84	0.94	-0.08	-0.18, 0.02
Y	62	0.95	65	0.94	0.01	-0.08, 0.11
W	58	0.93	61	0.98	-0.05	-0.15, 0.03

Seroconversion Rate:
SBA-BR

Serogroup (11-18 yrs old)	Menomune (Me)		Menactra (Ma)		Diff (Me-Ma)	95% CI for the Difference
	N	Proportion	N	Proportion		
A	11	1	12	1	0	-0.29, 0.27
C	62	0.9	57	0.95	-0.04	-0.15, 0.06
Y	39	0.9	41	0.93	-0.03	-0.18, 0.11
W	23	1	22	0.95	-0.05	-0.11, 0.23

SBA-H

Serogroup (11-18 yrs old)	Menomune (Me)		Menactra (Ma)		Diff (Me-Ma)	95% CI for the Difference
	N	Proportion	N	Proportion		
A	11	0.91	12	0.92	-0.01	-0.34, 0.31
C	62	0.82	57	0.91	-0.09	-0.22, 0.04
Y	39	0.92	41	0.93	-0.004	-0.15, 0.13
W	23	0.83	22	0.95	-0.13	-0.35, 0.08

18-55 year old:

SBA-BR

Serogroup	Menomune (Me)		Menactra (Ma)		Diff (Me-Ma)	95% CI
	N	Proportion	N	Proportion		
Seroresponse Rate						
	50	0.72	50	0.80	-0.08	-0.25, 0.09
	50	0.94	50	0.96	-0.02	-0.13, 0.08
Seroconversion Rate						
Y	17	0.88	18	1	-0.12	-0.37, 0.08
W	9	1	8	0.89	0.11	-0.26, 0.48

SBA-H:

Serogroup	Menomune (Me)		Menactra (Ma)		Diff (Me-Ma)	95% CI
	N	Proportion	N	Proportion		
Seroresponse Rate						
Y	50	1	50	0.96	0.04	-0.03, 0.14
W	50	1	50	1	0	-0.07, 0.07
Seroconversion Rate						
Y	17	1	18	0.89	0.11	-0.10, 0.35
W	9	1	8	1	0	-0.35, 0.37

4.0 Efficacy Data (Immunogenicity)

Immunogenicity data from the following clinical trials were the basis of inferring the efficacy of Menactra:

- **Study MTA-02:** A Comparative Trial of the Safety and Immunogenicity of Menactra versus Menomune® A/C/Y/W-135 in Adolescents 11-18 years old
- **Study MTA-09:** A Comparative Trial of the Safety and Immunogenicity of Menactra versus Menomune® A/C/Y/W-135 in Adults 18-55 years old

The primary endpoint, vaccine administration, surveillance, laboratory methods, and population for analysis were the same in both trials, as are described below:

Assessment of Immunogenicity:
The primary endpoint was the proportion of participants achieving a four-fold or greater increase in serum bactericidal antibody, to serogroups A, C, Y, and W135. Other parameters of immune response were also provided (seroconversion, GMT, geometric mean fold rise, reverse cumulative distribution curve, group-specific anti-meningococcal PS antibody measured by ELISA).

Vaccine Administration
Menactra was administered as a single dose intramuscularly.

Control vaccine
The active control vaccine implemented in both studies was 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. A single dose was administered subcutaneously.

Surveillance (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. In a subset of 160 MTA-02 participants, group-specific IgG and IgM antibody were measured by ELISA.

Laboratory Methods
All assays were performed at Aventis Pasteur, Inc.

Anti-Meningococcal Antibody Determination by Serum Bactericidal Assay
Functional antibody activity to each serogroup was determined using a serum bactericidal assay, which is an adaptation of the CDC method recommended by the WHO Expert Committee of the Department of Vaccines and Biologicals.[11,12] The lower limit of detection for this assay, using baby rabbit complement, is a titer of 1: 8.

IgG and IgM Anti-Meningococcal Antibody Determination
IgG and IgG antibody activity for anti-meningococcal antibody to serogroups A, C, Y, and W-135 was measured using an indirect ELISA.

Populations for Analysis
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. The primary analysis was based on the per-protocol population.

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.

4.1 Study MTA-02

Title: 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.

Immunogenicity Objectives

- Primary objective: To describe and compare the 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.
- 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®.

Design: The study was a randomized, modified double blind, multi-center, active-controlled trial. Participants were randomized in a 1: 1 (Menactra: Menomune®) ratio. Participants were enrolled at eleven study centers in the United States.

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

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 by the data if the upper limit of the one-sided 95% confidence interval (CI) of $p_{\text{Menomune®}} - p_{\text{Menactra}}$ 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. The sample size 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 demonstration of equivalence 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.

CBER recommendations for non-inferiority hypothesis testing have evolved since the conduct of this trial. Comparisons are currently based on the upper limit of the two-sided 95% confidence interval for the difference in two proportions.

Results

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. The per protocol population for immunogenicity 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%).

MTA-02: Primary Hypothesis Testing
Number and Proportion of Participants 11-18 Years Old with a >Four-fold Increase in SBA-BR Titer

Serogroup	Menomune® N= 423		Menactra N= 423		Difference ($p_{\text{Menomune®}} - p_{\text{Menactra}}$)	Upper Limit of the 1-sided 95% CI of the Difference§	Upper Limit of the 2-sided 95% CI of the Difference§
	n*	$p_{\text{Menomune®}}$†	n*	P_{Menactra}‡			
A	391	0.924	392	0.926	-0.002	0.027	0.033
C	375	0.886	388	0.917	-0.031	0.003	0.009
Y	339	0.801	346	0.818	-0.017	0.028	0.036
W-135	403	0.952	409	0.966	-0.014	0.008	0.013

*n: number of participants with = 4-fold rise from baseline SBA-BR titer. N: total number of participants with valid serology data.
† $p_{\text{Menomune®}}$: 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.

Serum bactericidal antibody:

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

Serogroup	Menomune® N= 423			Menactra 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.

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. In both groups, all participants with serogroup A SBA-BR antibody less than 1:8 pre-vaccination, 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 83% [138/139] of individuals who received Menomune®.

Serogroup-specific IgG and IgM antibody:
Serogroup-specific IgG and IgM antibody levels, measured by ELISA, were assessed in a subset of 161 participants [Menactra n=82, Menomune® n=79].

MTA-02: Comparison of Serogroup-specific IgG and SBA-BR GMT Post-vaccination

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 SBA-BR GMT analysis was based on 846 participants [Menactra n=423, Menomune® n=423] with valid serology data.

MTA-02: Serogroup-specific IgM Geometric Mean Concentrations Post-vaccination, with 95% CI

Serogroup	Vaccine Group	IgM (µg/mL)	95% CI
A	Menomune®	12.0	9.7, 14.9
	Menactra	17.8	14.7, 21.6
C	Menomune®	1.7	1.4, 2.1
	Menactra	1.6	1.2, 2.0
Y	Menomune®	3.5	2.9, 4.2
	Menactra	3.5	2.8, 4.3
W-135	Menomune®	1.7	1.4, 2.0
	Menactra	1.9	1.6, 2.3

4.2 Study MTA-09:

Title: 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.

Immunogenicity Objectives

?? Primary objective:

✍✍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 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®.

Design
The study was a randomized, modified double blind, multi-center, active-controlled trial. 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. Participants were enrolled at thirty-three study centers in the United States.

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

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

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 by the data if the upper bound of the two-sided 95% CI of $p_{\text{Menomune®}} - p_{\text{Menactra}}$ 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. The sample size 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: 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 $GMT_{\text{Menactra}}/GMT_{\text{Menomune}} < \log_2(2)$ 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.

Results
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. The per protocol population for immunogenicity included 1280 Menactra and 1098 Menomune® participants.

Immunogenicity population:
One hundred forty-six (Menactra n=84, Menomune® n=62) of 301participants 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.

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%).

MTA-09: Primary Hypothesis Testing
Number and Proportion of Participants 18-55 Years Old with a ≥ Four-fold Increase in SBA-BR Titer

Serogroup	Menomune® N= 1098		Menactra N= 1280		Difference ($p_{Menomune®}$ - $p_{Menactra}$)	Upper Limit of the 2-sided 95% CI of the Difference§
	n*	$p_{Menomune®}$†	n*	$p_{Menactra}$‡		
A	929	0.846	1030	0.805	0.041	0.072
C	985	0.897	1133	0.885	0.012	0.037
Y	872	0.794	941	0.735	0.059	0.093
W-135	1036	0.944	1144	0.894	0.050	0.072

*n: number of participants with = 4-fold rise in SBA-BR titer from baseline. N: total number of participants with valid serology data.
† $p_{Menomune®}$: 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.

Serum bactericidal antibody:

MTA-09: Number and Percentage of Participants 18-55 Years Old Achieving a ≥ Four-fold Increase in SBA-BR Antibody Titer, with 95%CI

Serogroup	Menomune® N= 1098			Menactra 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.

SBA-BR GMT:

MTA-09: SBA-BR Geometric Mean Antibody Titer Pre - and 28 days Post-vaccination

Serogroup	Timepoint	Menomune® N= 1098		Menactra N= 1280	
		SBA-BR GMT	95% CI	SBA-BR GMT	95% CI
A	Day 0	203.6	180.3, 229.9	223.8	200.1, 250.4
	Day 28	4114.1	3832.2, 4416.8	3896.9	3647.0, 4164.0
C	Day 0	51.7	45.4, 56.0	56.8	50.2, 64.4
	Day 28	3469.4	3148.4, 3823.1	3231.1	2954.9, 3533.2
Y	Day 0	127.2	111.8, 144.8	123.2	109.1, 139.0
	Day 28	2448.6	2237.0, 2680.2	1750.4	1597.0, 1918.5
W-135	Day 0	30.9	27.8, 34.4	33.1	29.9, 36.7
	Day 28	1871.2	1722.8, 2032.4	1271	1171.9, 1378.4

N: total number of participants with valid serology data.

SBA-BR geometric mean titer, using the baseline titer as a covariate:
The upper limit of the two-sided 95% CI for the anti-log of the treatment effect for each serogroup was less than $\log_2$ (2), which indicated that the post-vaccination SBA-BR GMT, for each serogroup, did not differ between the two vaccine groups when adjusted for baseline disparities in pre-existing antibody.

MTA-09: Treatment Effect on SBA-BR GMT, Adjusted by Baseline Covariate

Serogroup	Vaccine Group	Baseline SBA-BR GMT	Estimate of Baseline GMT Effect	Difference of the Treatment Effect (Menomune®- Menactra)	Anti-Log of Treatment Effect* (Menomune®- Menactra)	95% CI for Anti-Log of the Treatment Effect (Menomune®- Menactra)
A	Menomune®	203.6	-0.849	0.099	1.071	0.975, 1.177
	Menactra	223.8				
C	Menomune®	51.7	-0.771	0.134	1.097	0.968, 1.244
	Menactra	56.8				
Y	Menomune®	127.2	-0.743	0.472	1.387	1.229, 1.567
	Menactra	123.2				
W-135	Menomune®	30.9	-0.764	0.581	1.496	1.339, 1.672
	Menactra	33.1				

* Anti-Log of the treatment effect is calculated as 2 to the treatment effect (Menomune-Menactra) power.

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 after vaccination. All Menactra recipients with SBA-BR antibody titer less than 1:8 pre-vaccination, and 99.3% [143/144] of corresponding Menomune® recipients achieved this criterion for serogroup A. For serogroup C, seroconversion was observed in 99.4% [343/345] of Menactra recipients and 97.7% [297/304] of Menomune® recipients. For the remaining serogroups, 90.7% [253/279] and 96.5% [360/373] of Menactra participants responded with a ≥4-fold antibody rise to serogroups Y and W135, respectively, compared with 96.9% [221/228] and 99.1% [325/328] of individuals who received Menomune®.

5.0 Safety Data

The epidemiology of meningococcal disease in the United States and ACIP recommendations for the prevention of meningococcal disease among college freshmen projected frequent use of this vaccine in adolescents and young adults. Hence, particular attention was given to characterizing the safety profile in the 15-25 year old age group. The number of participants enrolled for all studies combined is summarized in the following table:

Overall Safety Database

Age group	# Participants enrolled	
	Menactra n	Menomune® n
11-14 years	1636	490
15-25 years	4078	1578
26-55 years	1957	973
Total for 11-55y*	**7672**	**3041**

Clinical studies MTA-04 and MTA-09 included non-inferiority comparisons of adverse events as a primary hypothesis, and studies MTA-02 and MTA-14 included safety comparisons as a secondary hypothesis. Study design elements that pertain to the safety assessment, and were uniform across all studies, are the following:

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

Monitored parameters:

- **Immediate reactions:** 30 minutes post-vaccination
- **Local and systemic adverse events:** reactogenicity was assessed during Days 0-7 (day of vaccination = Day 0). The events were recorded on a diary card, and also collected by study personnel through telephone interview eight days after vaccination. Pre-specified local reactions were erythema, swelling, induration, pain. In studies MTA-04, MTA-09, MTA-14, information was obtained for fever measured by oral temperature, headache, fatigue, chills, arthralgia, anorexia, vomiting, diarrhea, seizures, malaise and rash. If rash was reported, the investigator was prompted to record additional details on a separate case report form. In study MTA-02, which was conducted early in clinical development, the same systemic reactions were collected except for arthalgia and chills. The presence of rash was assessed qualitatively, but prompts for additional details were not included on the case report form.
- **Unsolicited adverse events:** Days 0-28. Information about these events was obtained by telephone interview eight and twenty-eight days after vaccination.
- **Significant adverse events:** Day 0- 6 months. These events consisted of visits to an emergency room, or unexpected visits to an office physician were collected via scripted telephone interview.
- **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.

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

Populations for analysis
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.

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.

5.1 Study MTA-04

Title: 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

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

Design

The study was a randomized, modified double blind, multi-center, active-controlled trial. Participants were enrolled at thirty-two study centers in the United States. Enrollment was stratified by 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.

Primary Endpoint:

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

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 Menactra and Menomune® groups, respectively. The sample size provided 80% power to achieve the primary hypothesis, assuming that the expected proportion of subjects with at least one systemic reaction in the Menomune group is 1%. Primary hypothesis testing was conducted at the 0.05 significance level. CBER recommendations for non-inferiority hypothesis testing have evolved since the conduct of this trial. Comparisons are currently based on the upper limit of the two-sided 95% confidence interval. The sponsor also included primary safety analysis results according to current CBER recommendations.

Although enrollment was stratified by two age groups (11-14 years, 15-18 years) to ensure adequate representation of participants in each age group, the analyses were based upon the total study population, regardless of stratified age group. In addition, all rashes occurring during the first 7 days after vaccination were designated, for the purpose of analysis, as a severe solicited systemic reaction.

Results

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. The intent-to-treat population for safety included 3242 participants (Menactra n=2270, Menomune® n= 972). Participants completing the safety assessment 6 months after vaccination are summarized in section 6.5.

Local Reactions

MTA-04: 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	9.7, 12.3	55	5.7	4.3, 7.3
< 1 inch	**Mild**	197	8.7	7.6, 9.9	51	5.3	3.9, 6.7
1 – 2 inches	**Moderate**	37	1.6	1.2, 2.3	4	0.4	0.1, 1.1
> 2 inches	**Severe**	13	0.6	0.3, 1.0	0	0	0.0, 0.3
Swelling							
	Any	245	10.8	9.6, 12.2	35	3.6	2.5, 5.0
< 1 inch	**Mild**	191	8.4	7.3, 9.7	32	3.3	2.3, 4.6
1 – 2 inches	**Moderate**	43	1.9	1.4, 2.6	3	0.3	0.1, 0.9
> 2 inches	**Severe**	11	0.5	0.2, 0.9	0	0	0.0, 0.3
Induration							
	Any	355	15.7	14.2, 17.2	50	5.2	3.9, 6.7
< 1 inch	**Mild**	292	12.9	11.5, 14.4	45	4.6	3.4, 6.2
1 – 2 inches	**Moderate**	56	2.5	1.9, 3.2	5	0.5	0.2, 1.2
> 2 inches	**Severe**	7	0.3	0.1, 0.6	0	0	0.0, 0.3
Pain							
	Any	1340	59.2	57.1, 61.2	278	28.7	25.8, 31.6
	Mild	1045	46.2	44.1, 48.2	253	26.1	23.3, 29.0
	Moderate	289	12.8	11.4, 14.2	25	2.6	1.7, 3.8
	Severe	6	0.3	0.1, 0.6	0	0	0.0, 0.3

*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

MTA-04: Systemic adverse reactions (Days 0-7)							
		Menactra			Menomune®		
		N= 2265			N= 970		
Reaction	Severity	n*	%†	95% CI	n*	%†	95% CI
Fever							
	Any	115	5.1	4.2, 6.1	29	3.0	2.0, 4.3
38.0ºC-38.9ºC	**Mild**	102	4.5	3.7, 5.4	25	2.6	1.7, 3.8
39.0ºC-39.9ºC	**Moderate**	13	0.6	0.3, 1.0	3	0.3	0.1, 0.9
≥ 40.0ºC	**Severe**	0	0.0	0.0, 0.1	1	0.1	0.0, 0.6
Headache							
	Any	807	35.6	33.7, 37.6	284	29.3	26.4, 32.3
	Mild	566	25.0	23.2, 26.8	217	22.4	19.8, 25.1
	Moderate	217	9.6	8.4, 10.9	63	6.5	5.0, 8.2
	Severe	24	1.1	0.7, 1.6	4	0.4	0.1, 1.1

Cont. MTA-04: Systemic adverse reactions (Days 0-7)							
		Menactra			Menomune®		
		N= 2265			N= 970		
Reaction	**Severity**	**n***	**%**	**95% CI**	**n***	**%**	**95% CI**
Fatigue							
	Any	679	30.0	28.1, 31.9	243	25.1	22.4, 27.9
	Mild	484	21.4	19.7, 23.1	181	18.7	16.3, 21.3
	Moderate	169	7.5	6.4, 8.6	60	6.2	4.8, 7.9
	Severe	26	1.1	0.8, 1.7	2	0.2	0.0, 0.7
Malaise							
	Any	496	21.9	20.2, 23.7	163	16.8	14.5, 19.3
	Mild	340	15.0	13.6, 16.6	126	13.0	10.9, 15.3
	Moderate	131	5.8	4.9, 6.8	33	3.4	2.4, 4.7
	Severe	25	1.1	0.7, 1.6	4	0.4	0.1, 1.1
Arthralgia							
	Any	394	17.4	15.9, 19.0	99	10.2	8.4, 12.3
	Mild	304	13.4	12.0, 14.9	78	8.0	6.4, 9.9
	Moderate	82	3.6	2.9, 4.5	20	2.1	1.3, 3.2
	Severe	8	0.4	0.2, 0.7	1	0.1	0.0, 0.6
Chills							
	Any	158	7.0	6.0, 8.1	34	3.5	2.4, 4.9
	Mild	115	5.1	4.2, 6.1	29	3.0	2.0, 4.3
	Moderate	38	1.7	1.2, 2.3	4	0.4	0.1, 1.1
	Severe	5	0.2	0.1, 0.5	1	0.1	0.0, 0.6
Anorexia							
	Any	243	10.7	9.5, 12.1	75	7.7	6.1, 9.6
Skips 1 meal	**Mild**	190	8.4	7.3, 9.6	62	6.4	4.9, 8.1
Skips 2 meals	**Moderate**	46	2.0	1.5, 2.7	11	1.1	0.6, 2.0
Skips ≥ 3 meals	**Severe**	7	0.3	0.1, 0.6	2	0.2	0.0, 0.7
Vomiting							
	Any	44	1.9	1.4, 2.6	14	1.4	0.8, 2.4
1 episode	**Mild**	29	1.3	0.9, 1.8	6	0.6	0.2, 1.3
2 episodes	**Moderate**	9	0.4	0.2, 0.8	5	0.5	0.2, 1.2
≥3 episodes	**Severe**	6	0.3	0.1, 0.6	3	0.3	0.1, 0.9
Diarrhea							
	Any	271	12.0	10.7, 13.4	99	10.2	8.4, 12.3
1-2 episodes	**Mild**	228	10.1	8.9, 11.4	86	8.9	7.2, 10.8
3-4 episodes	**Moderate**	36	1.6	1.1, 2.2	13	1.3	0.7, 2.3
≥ 5 episodes	**Severe**	7	0.3	0.1, 0.6	0	0.0	0.0, 0.3
Seizures (Y/N)							
Yes	**Days 0-3**	0	0.0	0.0, 0.1	0	0.0	0.0, 0.3
Yes	**Days 4-7**	0	0.0	0.0, 0.1	0	0.0	0.0, 0.3
Yes	**Days 0-7**	0	0.0	0.0, 0.1	0	0.0	0.0, 0.3
Rash							
Any rash	**Days 0-3**	23	1.0	0.6, 1.5	10	1.0	0.5, 1.9
Any rash	**Days 4-7**	23	1.0	0.6, 1.5	7	0.7	0.3, 1.5
Any rash	**Days 0-7**	37	1.6	1.2, 2.2	14	1.4	0.8, 2.4

*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.

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

Reviewer comment: Excluding rashes, 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. In the Menomune group, 3 of 12 (25%) participants reported two or more severe systemic reactions.

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

Primary Hypothesis Testing

The proportion of Menactra participants with at least one severe systemic reaction during Days 0-7 was 0.043 (4.3%) and 0.041 (4.1%) in the Menomune® group. The upper limit of the two-sided 90% CI, and 95% CI, for the difference in two proportions was 0.020 (2.0%), and 0.024 (2.4%), respectively.

MTA-04: Number and Proportion of Participants 11-18 Years Old With At Least One Severe Solicited Systemic Reaction

Menactra		Menomune®		Ratio $p_{Menactra}$ / $p_{Menomune®}$	Upper Limit of the 2-sided 90% CI‡ of the Ratio	Upper Limit of the 2-sided 95% CI‡ of the Ratio
N= 2265		N= 970				
n*	$p_{Menactra}$†	n*	$p_{Menomune®}$†			
97	0.043	25	0.026	1.7	2.4	2.6

*Number of participants with at least 1 severe systemic reaction or rash. N= Total number of participants for whom safety information is available.
†$p_{Menactra}$ and $p_{Menomune®}$: proportion 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.

Reviewer comment: Aside from rash, 24 of 61 (34%) Menactra participants reported more than one severe systemic adverse event (AEs), as follows: 5 severe AEs (two participants), 4 AEs (three participants), 3 AEs (nine participants), and 2 AEs (nine participants). For 3 Menactra participants, severe systemic reactions consisted of fatigue and malaise. In the Menomune group, 3 of 12 (25%) participants reported two or more severe systemic reactions. One participant reported 4, 3, and 2 severe AEs, respectively.

5.2 Study MTA-02

Title: 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.

(Please see section 5.1 for synopsis of study design. The primary objective pertained to immunogenicity)

Safety Objectives

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

?? Other objectives:
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®.

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

Statistical Plan
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 by the data 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. The definition of non-inferiority to Menomune® used for statistical hypothesis testing varied from the primary safety hypothesis in studies MTA-04 and MTA-09, and reflected ongoing discussions, between CBER and the sponsor, during the course of clinical development. The sponsor also included an additional analysis of the secondary endpoint, with two-sided 95% confidence intervals, which is the current CBER recommendation for non-inferiority hypothesis testing. All rashes occurring during the first 7 days after vaccination were designated, for the purpose of analysis, as a severe solicited systemic reaction.

Results
The proportion of Menactra participants with at least one severe systemic reaction during Days 0-7 was 0.039 [17/439] and 0.041 [18/441] in the Menomune® group. The upper limit of the two-sided 90% CI, and 95% CI, for the difference in two proportions was 0.020 (2.0%), and 0.024 (2.4%), respectively.

Participants completing the safety assessment 6 months after vaccination are summarized in section 6.5.

5.3 Study MTA-09

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

(Please see section 5.2 for synopsis of study design. This study contained both safety and immunogenicity primary objectives.)

Safety 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.

?? 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®.

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

Statistical plan
Primary Safety 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 (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 Menactra and Menomune® groups, respectively. The sample size provided 80% power to achieve the primary hypothesis, assuming that the expected proportion of subjects with at least one systemic reaction in the Menomune group is 1%. 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 requested safety endpoint was described as an additional analysis. All rashes occurring during the first 7 days after vaccination were designated, for the purpose of analysis, as a severe solicited systemic reaction.

Results
The intent-to-treat population for safety included 2530 participants (Menactra n=1371, Menomune® n= 1159). Participants completing the safety assessment 6 months after vaccination are summarized in section 6.5.

Local Reactions:

MTA-09: Local adverse reactions (Days 0-3, 4-7, 0-7)

			Menactra			Menomune®		
			N= 1371			N= 1159		
Reaction	**Severity**		**n***	**%†**	**95% CI**	**n***	**%†**	**95% CI**
Redness								
	Any	Days 0-3	196	14.3	12.5, 16.3	185	16.0	13.9, 18.2
		Days 4-7	47	3.4	2.5, 4.5	5	0.4	0.1, 1.0
		Days 0-7	198	14.4	12.6, 16.4	185	16.0	13.9, 18.2
< 1 inch	**Mild**	Days 0-3	144	10.5	8.9, 12.3	162	14.0	12.0, 16.1
		Days 4-7	25	1.8	1.2, 2.7	4	0.3	0.1, 0.9
		Days 0-7	143‡	10.4	8.9, 12.2	162	14.0	12.0, 16.1
1 – 2 inches	**Moderate**	Days 0-3	37	2.7	1.9, 3.7	22	1.9	1.2, 2.9
		Days 4-7	18	1.3	0.8, 2.1	1	0.1	0.0, 0.5
		Days 0-7	40	2.9	2.1, 4.0	22	1.9	1.2, 2.9
> 2 inches	**Severe**	Days 0-3	15	1.1	0.6, 1.8	1	0.1	0.0, 0.5
		Days 4-7	4	0.3	0.1, 0.8	0	0.0	0.0, 0.3
		Days 0-7	15	1.1	0.6, 1.8	1	0.1	0.0, 0.5

Cont. MTA-09: Local adverse reactions (Days 0-3, 4-7, 0-7)								
			Menactra			Menomune®		
			N= 1371			N= 1159		
Reaction	Severity		n*	% †	95% CI	n*	% †	95% CI
Swelling								
	Any	Days 0-3	171	12.5	10.8, 14.3	86	7.4	6.0, 9.1
		Days 4-7	36	2.6	1.9, 3.6	3	0.3	0.1, 0.8
		Days 0-7	173	12.6	10.9, 14.5	88	7.6	6.1, 9.3
< 1 inch	**Mild**	Days 0-3	127	9.3	7.8, 10.9	78	6.7	5.4, 8.3
		Days 4-7	24	1.8	1.1, 2.6	3	0.3	0.1, 0.8
		Days 0-7	128	9.3	7.9, 11.0	80	6.9	5.5, 8.5
1 – 2 inches	**Moderate**	Days 0-3	31	2.3	1.5, 3.2	8	0.7	0.3, 1.4
		Days 4-7	9	0.7	0.3, 1.2	0	0.0	0.0, 0.3
		Days 0-7	32	2.3	1.6, 3.3	8	0.7	0.3, 1.4
> 2 inches	**Severe**	Days 0-3	13	0.9	0.5, 1.6	0	0.0	0.0, 0.3
		Days 4-7	3	0.2	0.1, 0.6	0	0.0	0.0, 0.3
		Days 0-7	13	0.9	0.5, 1.6	0	0.0	0.0, 0.3
Induration								
	Any	Days 0-3	233	17.0	15.0, 19.1	125	10.8	9.1, 12.7
		Days 4-7	49	3.6	2.7, 4.7	6	0.5	0.2, 1.1
		Days 0-7	235	17.1	15.2, 19.2	127	11.0	9.2, 12.9
< 1 inch	**Mild**	Days 0-3	180	13.1	11.4, 15.0	113	9.7	8.1, 11.6
		Days 4-7	33	2.4	1.7, 3.4	5	0.4	0.1, 1.0
		Days 0-7	179‡	13.1	11.3, 15.0	115	9.9	8.3, 11.8
1 – 2 inches	**Moderate**	Days 0-3	44	3.2	2.3, 4.3	12	1.0	0.5, 1.8
		Days 4-7	13	0.9	0.5, 1.6	1	0.1	0.0, 0.5
		Days 0-7	47	3.4	2.5, 4.5	12	1.0	0.5, 1.8
> 2 inches	**Severe**	Days 0-3	9	0.7	0.3, 1.2	0	0.0	0.0, 0.3
		Days 4-7	3	0.2	0.1, 0.6	0	0.0	0.0, 0.3
		Days 0-7	9	0.7	0.3, 1.2	0	0.0	0.0, 0.3
Pain								
	Any	Days 0-3	736	53.7	51.0, 56.4	556	48.0	45.1, 50.9
		Days 4-7	82	6.0	4.8, 7.4	7	0.6	0.2, 1.2
		Days 0-7	739	53.9	51.2, 56.6	558	48.1	45.2, 51.1
	Mild	Days 0-3	578	42.2	39.5, 44.8	518	44.7	41.8, 47.6
		Days 4-7	73	5.3	4.2, 6.7	6	0.5	0.2, 1.1
		Days 0-7	581	42.4	39.7, 45.0	519	44.8	41.9, 47.7
	Moderate	Days 0-3	155	11.3	9.7, 13.1	37	3.2	2.3, 4.4
		Days 4-7	9	0.7	0.3, 1.2	1	0.1	0.0, 0.5
		Days 0-7	155	11.3	9.7, 13.1	38	3.3	2.3, 4.5
	Severe	Days 0-3	3	0.2	0.1, 0.6	1	0.1	0.0, 0.5
		Days 4-7	0	0.0	0.0, 0.2	0	0.0	0.0, 0.3
		Days 0-7	3	0.2	0.1, 0.6	1	0.1	0.0, 0.5

*n: number of participants reporting at least one event in this category. Thirteen Menactra and 11 Menomune participants did not provide any information. Percentages were based on the total number of participants who did provide 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

MTA-09: Injection Site Pain, Participants 18-25 & 22-55 years old, Days 0-7					
		Menactra		Menomune®	
Local Pain	Severity	%	95% CI	%	95% CI
Age 18-25 years	Any	61.1	57.5, 64.5	51.8	47.9, 55.6
	Mild	45.8	42.3, 49.4	47.9	44.1, 51.8
	Moderate	15.2	12.9, 18.0	3.7	2.5, 5.5
	Severe	0.0	0.0, 0.0	0.2	0.0, 0.9
Age 26-55 years	Any	45.1	41.2, 49.1	43.6	39.4, 47.9
	Mild	38.2	34.4, 42.1	40.9	36.7, 45.2
	Moderate	6.5	4.8, 8.7	2.7	1.6, 4.5
	Severe	0.5	0.8, 1.4	0.0	0.0, 0.8

*n: number of participants reporting at least one event in this category. N= Total number of participants for whom safety information is available for this 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:

MTA-09: Systemic adverse reactions (Days 0-7)							
		Menactra			Menomune®		
		N= 1371			N= 1159		
Reaction	Severity	n*	%†	95% CI	n*	%†	95% CI
Fever							
	Any	21	1.5	1.0, 2.3	6	0.5	0.2, 1.1
38.0ºC-38.9ºC	Mild	17	1.2	0.7, 2.0	5	0.4	0.1, 1.0
39.0ºC-39.9ºC	Moderate	4	0.3	0.1, 0.8	1	0.1	0.0, 0.5
≥ 40.0ºC	Severe	0	0	0.0, 0.2	0	0	0.0, 0.3
Headache							
	Any	568	41.4	38.8, 44.1	484	41.8	38.9, 44.7
	Mild	414	30.2	27.8, 32.7	370	31.9	29.3, 34.7
	Moderate	138	10.1	8.5, 11.8	103	8.9	7.3, 10.7
	Severe	16	1.2	0.7, 1.9	11	0.9	0.5, 1.7
Fatigue							
	Any	476	34.7	32.2, 37.3	374	32.3	29.6, 35.1
	Mild	350	25.5	23.2, 27.9	293	25.3	22.8, 27.9
	Moderate	114	8.3	6.9, 9.9	76	6.6	5.2, 8.1
	Severe	12	0.9	0.5, 1.5	5	0.4	0.1, 1.0
Malaise							
	Any	324	23.6	21.4, 26.0	259	22.3	20.0, 24.9
	Mild	219	16	14.1, 18.0	195	16.8	14.7, 19.1
	Moderate	90	6.6	5.3, 8.0	54	4.7	3.2, 6.0
	Severe	15	1.1	0.6, 1.8	10	0.9	0.4, 1.6
Chills							
	Any	133	9.7	8.2, 11.4	65	5.6	4.4, 7.1
	Mild	96	7.0	5.7, 8.5	53	4.6	3.4, 5.9
	Moderate	29	2.1	1.4, 3.0	12	1	0.5, 1.8
	Severe	8	0.6	0.3, 1.2	0	0	0.0, 0.3
Arthralgia							
	Any	272	19.8	17.8, 22.1	185	16	13.9, 18.2
	Mild	204	14.9	13.0, 16.9	154	13.3	11.4, 15.4
	Moderate	64	4.7	3.6, 5.9	30	2.6	1.8, 3.7
	Severe	4	0.3	0.1, 0.8	1	0.1	0.0, 0.5

Cont. MTA-09: Systemic adverse reactions (Days 0-7)							
		Menactra			Menomune®		
		N= 1371			N= 1159		
Reaction	**Severity**	**n***	**% †**	**95% CI**	**n***	**% †**	**95% CI**
Anorexia							
	Any	162	11.8	10.2, 13.6	115	9.9	8.3, 11.8
Skips 1 meal	**Mild**	125	9.1	7.7, 10.8	91	7.9	6.4, 9.6
Skips 2 meals	**Moderate**	32	2.3	1.6, 3.3	19	1.6	1.0, 2.6
Skips ≥ 3 meals	**Severe**	5	0.4	0.1, 0.9	5	0.4	0.1, 1.0
Vomiting							
	Any	32	2.3	1.6, 3.3	17	1.5	0.9, 2.3
1 episode	**Mild**	24	1.8	1.1, 2.6	10	0.9	0.4, 1.6
2 episodes	**Moderate**	5	0.4	0.1, 0.9	2	0.2	0.0, 0.6
≥3 episodes	**Severe**	3	0.2	0.1, 0.6	5	0.4	0.1, 1.0
Diarrhea							
	Any	219	16	14.8, 18.0	162	14	12.0, 16.1
1-2 episodes	**Mild**	178	13	11.3, 14.9	124	10.7	9.0, 12.6
3-4 episodes	**Moderate**	36	2.6	1.9, 3.6	34	2.9	2.0, 4.1
≥ 5 episodes	**Severe**	5	0.4	0.1, 0.9	4	0.3	0.1, 0.9
Seizures (Y/N)							
Yes	**Days 0-3**	0	0	0.0, 0.2	0	0	0.0, 0.3
Yes	**Days 4-7**	0	0	0.0, 0.2	0	0	0.0, 0.3
Yes	**Days 0-7**	0	0	0.0, 0.2	0	0	0.0, 0.3
Rash							
Any rash	**Days 0-3**	15	1.1	0.6, 1.8	7	0.6	0.2, 1.2
Any rash	**Days 4-7**	10	0.7	0.4, 1.3	3	0.3	0.1, 0.8
Any rash	**Days 0-7**	19	1.4	0.8, 2.2	9	0.8	0.4, 1.5

*n: number of participants reporting at least one event in this category. Thirteen Menactra and 11 Menomune participants did not provide any information. Percentages were based on the total number of participants who did provide 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

Primary Hypothesis Testing

The proportion of Menactra participants with at least one severe systemic reaction during Days 0-7 was 0.038 (3.8%) and 0.026 (2.6%) in the Menomune® group. The upper limit of the two-sided 90% CI, and 95% CI, for the difference in two proportions was 0.021 (2.1%), and 0.023 (2.3%), respectively.

MTA-09: Number and Proportion of Participants 18-55 Years Old With At Least One Severe Solicited Systemic Rxn						
Menactra		Menomune®				
N= 1371		N= 1159				
n*	**$p_{Menactra}$†**	**n***	**$p_{Menomune®}$†**	**Ratio $p_{Menactra}$ / $p_{Menomune®}$**	**Upper Limit of the 2-sided 90% CI‡ of the Ratio**	**Upper Limit of the 2-sided 95% CI‡ of the Ratio**
52	0.038	30	0.026	1.5	2.1	2.3

*n: Number of participants with at least 1 severe systemic reaction or rash. N= Total number of participants for whom safety information is available.
†$p_{Menactra}$ and $p_{Menomune®}$: proportion 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.

Reviewer comment: Aside from rash, 15 of 35 (43%) Menactra participants reported more than one severe systemic adverse event (AEs), as follows: 7 severe AEs (one participant), 5 AEs (one participant), 4 AEs (two participants), 3 AEs (seven participants), and 2 AEs (four participants). For 2 Menactra participants, severe systemic reactions consisted of fatigue and malaise. In the Menomune group, 8 of 23 (36%) participants reported two or more severe systemic reactions, as follows: 5 severe AEs (one participant), 4 AEs (two participants), 3 AEs (three participants), and 2 AEs (two participants).

5.4 Study MTA-14

Title: A Trial of the Lot Consistency of an Experimental Tetravalent (A, C, Y, and W-135) Meningococcal Diphtheria Toxoid Conjugate Vaccine Among Healthy U.S. Adults

Safety Objectives (The primary objective pertained to immunogenicity)

- Secondary objectives:
  - To compare the safety profile of each Menactra vaccine lot
  - To compare the safety profile for Menactra (3 lots combined) and Menomune® participants 26-55 years old
- Other objectives:
  - To describe the safety profile of each Menactra vaccine lot
  - To describe any relationship between post-vaccination reactogenicity and elevated pre-vaccination SBA-BR titer in all participants who receive Menactra

Design: The study was a randomized (1:1:1 for each Menactra lot), modified double blind, multi-center trial. An active control group was also included to enable safety comparisons in the 26-55 year old group, and enrollment was stratified by age to ensure adequate representation of participants for the safety assessment. Participants 18-25 years old were randomized to receive one of three Menactra vaccine, and participants 26-55 years old were randomized to receive either Menactra (lots 1, 2, or 3) or Menomune®. The study was conducted at twenty-four study centers in the United States.

Secondary Endpoints:

- The proportion of participants who experience at least one systemic reaction reported as severe during the 7-day period following vaccination is similar among the three vaccine lots.
- The proportion of participants 26-55 years old (3 Menactra lots combined) who experience at least one systemic reaction reported as severe during the 7-day period following vaccination.

Statistical plan (The primary hypothesis and secondary hypothesis #2 pertained to immunogenicity)
Secondary Hypotheses:
Secondary Hypothesis #1:
To demonstrate that the proportion of participants who experience at least one systemic reaction reported as severe during the 7 day period following vaccination is similar among the three vaccine lots.

This hypothesis would be supported by the data if the upper limit of the 2-sided 95% CI of $p_{max} - p_{min} < 0.1$, where p_{max} and p_{min} are the maximum and minimum proportion of participants with safety responses following vaccination with one of three Menactra vaccine lots.

Secondary Hypothesis #3:
To demonstrate that the safety response among 26-55 year old participants in the three Menactra groups is non-inferior to Menomune®, as measured by the proportion of participants who experience at least one 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 2-sided 95% CI of the difference in two proportions is less than 0.1. For this analysis, safety data from all Menactra participants 26-55 years old (lots #1-3) were combined and compared to data from age-matched Menomune® recipients.

Results
A total of 2040 (Menactra lot 1 n= 527, Menactra lot 2 n= 528, Menactra lot 3 n= 527, Menomune® n= 458) adults were enrolled, and 1886 (Menactra lot 1 n= 491, Menactra lot 2 n= 480, Menactra lot 3 n= 490, Menomune® n= 425) individuals completed the study. The intent-to-treat population for safety, for the Menactra lot consistency comparisons, included 1582 participants (Menactra lot 1 n= 527, lot 2 n= 528, lot 3 n= 527). Participants completing the safety assessment 6 months after vaccination are summarized in section 6.5.

Secondary Hypothesis #1
The proportion of Menactra vaccine lot #1, #2, and #3. with at least one severe systemic reaction during Days 0-7 was 0.035 [18/521], 0.033 [17/521] and 0.027 [14/522], respectively. The upper limit of the two-sided 95% CI for the difference in maximum and minimum proportions was 0.03 (3.0%).

Secondary Hypothesis #3
The proportion of Menactra participants 26-55 years old with at least one severe systemic reaction during Days 0-7 was 0.022 [15/685] and 0.055 [25/455] in the Menomune® group. The upper limit of the two-sided 95% CI, for the difference in two proportions was -0.01 (-1.0%).

5.5 SAEs and safety assessment 6 months post-vaccination

The number of subjects completing the safety assessment 6 months post-vaccination for studies MTA-02, -04, -09, and –14 is summarized in the following table:

Overall Participant Safety Profile		
	Menactra	**Menomune**
ITT population for safety*	**7670 (100%)**	**3041 (100%)**
Completed 28 day follow-up	**7500 (98%)**	**3004 (99%)**
Long-term safety follow-up obtained	5676 (100%)	3041 (100%)
Completed 6 month follow-up	**5453 (96%)**	**2923 (96%)**
MTA-02: 11-18 years old	436	435
MTA-04: 11-18 years old	2251	962
MTA-09: 18-55 years old	1301	1099
MTA-14: 18-55 years old	1464	427

Reviewer comment: No apparent increase in the frequency of newly diagnosed asthma, diabetes mellitus, or autoimmune disease was observed based on the data available.

Serious Adverse Events

Two deaths unrelated to vaccination occurred in study MTA-14. A 25-year old woman, who received Menactra lot #3, died in a motor vehicle accident 109 days after vaccination. The second participant, a 35-year old man, developed cardiopulmonary arrest approximately two hours after drug ingestion, and died at home on the same day. The emergency medical service had not been contacted, and details regarding the type of drug and how the body was discovered were not provided. The event occurred 72 days after Menomune® vaccination.

One SAE was reported by the investigator as possibly related to vaccination. A 17- year old Menactra participant, in study MTA-04, developed severe esophagitis and was hospitalized six days following immunization. A plausible cause for the event included a history of a sports-related back injury, four weeks prior to enrollment, and extended NSAID use thereafter. The event was thus considered by the CBER clinical reviewer as unlikely related to vaccination.

6.0 Concurrent Immunizations

Concurrent immunizations with two vaccines, Typhim Vi® and Td, was assessed in two separate studies.

6.1 Study MTA-11

Title: Immunogenicity and Safety of Typhoid Vi® Vaccine When Administered Concomitantly with an Experimental Tetravalent (A, C, Y, and W-135) Meningococcal Diphtheria Toxoid Conjugate Vaccine in Adults in the U.S.

Objectives

?? Primary objectives:

1. To compare the post-vaccination antibody level to typhoid Vi polysaccharide antigen (anti-Vi PS), when Typhim Vi® vaccine is co-administered with a saline placebo or with Menactra.
2. To compare the bactericidal antibody response to serogroups A, C, Y, W135, using baby rabbit complement (SBA-BR), when Menactra is co-administered with Typhim Vi®, to the corresponding antibody response when Menactra is given 28 days after Typhim Vi®.

?? Secondary objectives:

1. To compare the post-vaccination antibody level to Typhoid Vi antigen, when Typhim Vi® vaccine is co-administered with a saline placebo or with Menactra.
2. To compare the bactericidal antibody titer to serogroups A, C, Y, W135, using baby rabbit complement (SBA-BR), when Menactra is co-administered with Typhim Vi®, to the corresponding antibody response when Menactra is given 28 days after Typhim Vi®

?? Other objectives:

- To describe the SBA-BR titer to each serogroup, pre- and 28 days post-vaccination, in each vaccine group
- To describe the anti-Vi PS antibody level, pre- and 28 days post-vaccination, in each vaccine group
- To describe the distribution of participants with at least a 4-fold increase in anti-Vi PS antibody level, when Typhim Vi® vaccine is co-administered with a saline placebo or with Menactra.

Design

The study was a randomized, double blind, multi-center, controlled trial. Participants were randomized in a 1: 1 ratio (Menactra + Vi: Vi, then Menactra). Participants were enrolled at twelve study centers in the United States.

Vaccine administration

Each group received two injections 28 days apart. Group A received Typhim Vi® + Menactra, then a saline placebo. Group B received Typhim Vi® + saline placebo, followed by Menactra. Participants received all injections intramuscularly.

The typhoid Vi polysaccharide vaccine, Typhim Vi®, is commercially available in the United States. Each 0.5ml dose contains 25 µg of purified Vi polysaccharide, isotonic phosphate buffered saline, and

0.25% phenol, which is added as a preservative. The vaccine also contains residual polydimethylsiloxane or fatty acid ester based antifoam. The vaccine is formulated as a clear colorless solution, and packaged in a unit dose syringe.

Buffered Sterile Normal Saline (0.9% NaCl) was utilized as the placebo.

Primary Endpoints:

- The proportion of participants who achieve a protective level of anti-Vi polysaccharide antibody when Typhim Vi® vaccine is given together with a saline placebo, followed by Menactra 28 days later.
- The proportion of participants with at least a 4-fold rise in SBA-BR antibody titer to serogroups A, C, Y, and W-135 in the Typhim Vi®+ Menactra group is non-inferior to the proportion in the group receiving Typhim Vi® + placebo, followed by Menactra 28 days later.

Secondary endpoints:

- Anti-Vi PS antibody titer among these recipients is non-inferior to the same parameter among the group given Typhim Vi® + placebo, followed by Menactra 28 days later.
- SBA-BR antibody titer for serogroups A, C, Y, and W135 in the group receiving a staggered dosing regimen of Menactra and Typhoid Vi® vaccines is non-inferior to the same parameter in the group receiving the two vaccines concomitantly.

Surveillance

Monitored parameters:

Safety: Study participants were monitored for immediate reactions 30 minutes after 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), which were assessed after each vaccination. These events were recorded daily on a diary card, and also collected by study personnel through telephone interview eight days after each 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 each vaccination. Serious adverse events were reported and recorded during the entire study duration.

Efficacy (Immunogenicity):

Serum samples were obtained pre- and 28 days after each vaccination.

Anti-Meningococcal Antibody

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.

Anti-Vi Polysaccharide Antibody

Anti-Vi polysaccharide antibody was measured by a radioimmunoassay (RIA), according to a "Farr" type radioimmunologic method. Antibodies present in the blood sample bind to an Iodine 125 labeled Vi antigen, and form an immunological complex, which is then precipitated by an ammonium sulfate solution. The radioactivity measured in the precipitate is proportional to the quantity of Vi antibodies present in the sample.

Statistical plan

Primary Hypotheses:

Primary Hypothesis #1:

To demonstrate that 28 days following concomitant vaccination with Typhim Vi® vaccine (Vi) and Menactra, the proportion of participants who achieve a protective level of anti-Vi polysaccharide (Vi PS)

antibody is non-inferior to the proportion of participants who achieve a protective level of anti-Vi polysaccharide antibody when Typhim Vi® vaccine is given together with a saline placebo, followed by Menactra 28 days later.

This hypothesis would be supported by the data if the upper bound of the two-sided 95% CI of the difference $p_{\text{Vi + placebo}} - p_{\text{Vi + Menactra}} < 0.1$, where p is the proportion of participants, in the [Vi + placebo, then Menactra] and [Vi + Menactra] groups, respectively, who achieve an anti-Vi antibody level $\geq$1 µg/mL. The sample size provided 99.9% power to achieve the primary hypothesis. Testing of the primary hypothesis was conducted at the 0.025 significance level.

Primary Hypothesis #2:
To demonstrate that 28 days post-vaccination with Menactra, the proportion of participants with at least a 4-fold rise in SBA-BR antibody titer to serogroups A, C, Y, and W-135 in the Typhim Vi® + Menactra group is non-inferior to the proportion in the group receiving Typhim Vi® + placebo, followed by Menactra 28 days later.

This hypothesis would be supported by the data if the upper bound of the two-sided 95% CI of $p_{\text{Menactra}} - p_{\text{Vi + Menactra}} < 0.1$, where $_P$ is the proportions of participants with at least a 4-fold rise in SBA-BR antibody to meningococcal serogroups A, C, Y, and W-135, in the [Vi + placebo, then Menactra] and [Vi +Menactra] groups, respectively. The sample size provided at least 94% power to achieve the primary hypothesis for each serogroup. All tests of the primary hypothesis were conducted at the 0.025 significance level.

The primary analyses were based on data generated from the per-protocol population.

Secondary Hypotheses:
Secondary Hypothesis #1:
To demonstrate that 28 days following concomitant vaccination with Typhim Vi® vaccine and Menactra, the anti-Vi PS antibody titer among these recipients is non-inferior to the same parameter among the group given Typhim Vi® + placebo, followed by Menactra 28 days later.

This hypothesis would be supported by the data if the upper bound of the two-sided 95% CI of the ratio of $GMT_{\text{Vi + placebo}} / GMT_{\text{Vi + Menactra}} < 2$.

Secondary Hypothesis #2:
To demonstrate that 28 days after vaccination with Menactra, the SBA-BR antibody titer for serogroups A, C, Y, and W135 in the group receiving a staggered dosing regimen of Menactra and Typhoid Vi® vaccines is non-inferior to the same parameter in the group receiving the two vaccines concomitantly.

This hypothesis would be supported by the data if the upper bound of the two-sided 95% CI of the ratio of $GMT_{\text{Menactra}} / GMT_{\text{Vi + Menactra}} < 2$, where GMT_{Menactra} and $GMT_{\text{Vi + Menactra}}$ are the proportion of participants with at least a 4-fold rise in SBA-BR antibody to meningococcal serogroups A, C, Y, and W-135, in the Vi + placebo and Vi + Menactra groups, respectively. The statistical methods include an analysis of covariance with the baseline outcome as a covariate. The post-vaccination SBA-BR GMTs are calculated as a $\log_2$ titer.

Per-protocol population for immunogenicity:
The per-protocol population included all eligible participants who received the assigned vaccine at visits 1 & 2, 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 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.

All rashes occurring during the first 7 days after vaccination were designated, for the purpose of analysis, as a severe solicited systemic reaction.

Results

The group given Typhim Vi® (Vi) co-administered with Menactra, is designated Group A. The group receiving a staggered vaccination schedule [Vi + saline placebo, then Menactra 28 days later] is designated Group B. A total of 945 (Group A n= 469, Group B n= 476) adults were enrolled, and 871 (Group A n= 432, Group B n= 439) individuals completed the study.

Safety population:

The intent-to-treat population for safety included all enrolled participants (n= 945).

Immunogenicity population:

The per-protocol population included 839 participants (Group A n=419, Group B n=420).

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 (73.2%), but also included African American (10.6%), Hispanic (11.4%), Asian populations (3.1%) and individuals with mixed racial background (1.7%).

Immunogenicity

Antibody response to Vi Polysaccharide (Vi PS):

MTA-11: Number and Proportion of Participants 18-55 Years Old With Anti-Vi PS Antibody Level ≥ 1.0 ug/ml Post-vaccination

	Vi + Placebo, Then Menactra		Vi + Menactra Then Placebo		Difference ($p_{Vi + Placebo}$ - $p_{Vi + Menactra}$)	Upper Limit of the 2-sided 95% CI for the Difference§
	N=418		N=418			
	n*	$p_{Vi + Placebo}$†	n*	$p_{Vi + Menactra}$‡		
Vi PS antibody ≥1.0 µg/mL	331	0.792	342	0.818	-0.026	0.027

* n: number of participants with anti-Vi PS antibody titer ≥ 1.0 µg/mL. N: total number of participants with valid serology results on Day 28.

† $p_{Vi + Placebo}$: proportion of participants with anti-Vi PS antibody titer ≥ 1.0 µg/mL in the group given Typhim Vi® vaccine together with a saline placebo, and then Menactra 28 days later.

‡ $p_{Vi + Menactra}$: proportion of participants with anti-Vi PS antibody titer ≥ 1.0 µg/mL in the group given Typhim Vi® concomitantly with Menactra.

§ CI: Confidence interval.

Proportions with four-fold or greater increases in SBA-BR titer:

MTA-11: Number and Proportion of Participants 18-55 Years Old with a = 4-Fold Increase in SBA-BR Antibody Titers on Day 28, compared to Baseline

Serogroup	Vi + Placebo, Then Menactra		Vi + Menactra Then Placebo		Difference ($p_{Menactra}$ - $p_{Vi + Menactra}$)	Upper Limit of the 2-sided 95% CI for the Difference
	N=419		N=418			
	n*	$p_{Menactra}$†	n*	$p_{Vi + Menactra}$‡		
A	315	0.752	333	0.797	-0.045	0.012
C	370	0.883	374	0.895	-0.012	0.031
Y	273	0.657	311	0.744	-0.093	-0.031
W-135	351	0.838	356	0.852	-0.014	0.035

* n: number of participants with a ≥ 4-fold increase in SBA-BR titer compared with baseline. N: total number of participants with valid serology results on Day 28.

† %: proportion of participants with a = 4-fold rise from baseline SBA titer in the group given a staggered vaccine or concomitant vaccine regimen, respectively.

Vi PS GMT:

MTA-11: Comparison of Vi PS GMT, measured on Day 28 Following Typhim Vi® Vaccination						
	Vi + Placebo, Then Menactra		Vi + Menactra Then Placebo		Ratio of $GMT_{Vi + Placebo}$ / $GMT_{Vi + Menactra}$	Upper Limit of the 2-sided 95% CI for the GMT Ratio
	N=418		N=418			
	GMT	95% CI	GMT	95% CI		
Vi PS GMT	2.07	1.86, 2.32	2.4	2.15, 2.69	0.86	1.0

SBA-BR GMT: At baseline, the proportion of control group recipients with a SBA-BR titer ≥1:8 to serogroups A, C, Y and W-135 was 87% [365/419], 69% [289/419], 79% [329/419], and 54% [227/419], respectively. The respective proportions in the concomitant vaccine group were 79% [330/418], 64% [267/418], 71% [298/418], and 50% [208/418].

MTA-11: SBA-BR GMT 28 days after Menactra vaccination				
	Group B		Group A	
	Vi + Placebo, then Menactra		Vi + Menactra then placebo	
	N= 420		N= 419	
	GMT	95% CI	GMT	95% CI
Serogroup A				
SBA-BR GMT Day 0	336.9	274.2, 414.0	174.2	137.1, 221.5
SBA-BR GMT (28d post-)	5109.8	4523.3, 5772.4	5137.9	4490.4, 5878.9
Serogroup C				
SBA-BR GMT Day 0	47.6	38.2, 59.4	34.8	28.2, 42.9
SBA-BR GMT (28d post-)	3145.4	2635.1, 3754.6	3061.3	2525.2, 3711.4
Serogroup Y				
SBA-BR GMT Day 0	159.0	127.5, 198.2	97.7	78.1, 122.2
SBA-BR GMT (28d post-)	1742.2	1455.4, 2085.5	1821	1534.4, 2161.2
Serogroup W135				
SBA-BR GMT Day 0	20.0	16.6, 24.1	18.7	15.4, 22.6
SBA-BR GMT (28d post-)	929	750.3, 1150.3	1002	81.4, 88.3

N: total number of participants with valid serology results on Day 28.

Comparison of Log_2 SBA-BR Titer, using baseline titer as a covariate

MTA-11: Comparison of Log_2 SBA-BR Titer, measured on Day 28 Following Menactra Vaccination, using the Log_2 Baseline SBA Titer as a Covariate				
Serogroup	Vi + Placebo, Then Menactra	Vi + Menactra Then Placebo	Difference (Log_2 $SBA_{Menactra}$ - Log_2 $SBA_{Vi + Menactra}$)	Upper Limit of the 2-sided 95% CI for the Difference
	Log_2 $SBA_{Menactra}$†	Log_2 $SBA_{Vi + Menactra}$‡		
A	4.336	4.465	-0.129	0.13
C	6.210	6.292	-0.082	0.28
Y	3.704	3.969	-0.265	0.07
W-135	5.563	5.710	-0.147	0.25

† Log_2 $SBA_{Menactra}$: proportion of participants, with at least a 4-fold rise in SBA-BR antibody to meningococcal serogroups A, C, Y, and W-135, in the group given Typhim Vi® vaccine together with a saline placebo, and then Menactra 28 days later.

‡ Log_2 $SBA_{Vi + Menactra}$: proportion of participants, with at least a 4-fold rise in SBA-BR antibody to meningococcal serogroups A, C, Y, and W-135, in the group given Typhim Vi® concomitantly with Menactra.

Note: If the upper 95% CI of the difference is less than log2 (2) = 1, the inferiority assumption is rejected.

Safety

Local reactions following first vaccination:

The following table presents local adverse reactions, at the Menactra and Vi injection sites, in the same participant:

MTA-11: Local adverse reactions after the 1st Vaccination (Days 0-7):
Menactra (Group A) and Vi (Group A) injection sites

		Group A; N=456			**Group A; N=456**		
		Vi + **Menactra,** Then Placebo			**Vi** + Menactra, Then Placebo		
		(Menactra Injection site)			**(Typhim Vi Injection site)**		
Reaction	**Severity**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Redness							
	Any	52	11.4	8.6, 14.7	64	14.0	11.0,17.6
< 1 inch	**Mild**	32	7.0	4.8, 9.8	52	11.4	8.6,14.7
1 – 2 inches	**Moderate**	16	3.5	2.0, 5.6	12	2.6	1.4,4.6
> 2 inches	**Severe**	4	0.9	0.2, 2.2	0	0.0	0.0,0.8
Swelling							
	Any	61	13.4	10.4, 16.8	68	14.9	11.8,18.5
< 1 inch	**Mild**	44	9.6	7.1, 12.7	60	13.2	10.2,16.6
1 – 2 inches	**Moderate**	14	3.1	1.7, 5.1	7	1.5	0.6,3.1
> 2 inches	**Severe**	3	0.7	0.1, 1.9	1	0.2	0.0,1.2
Induration							
	Any	78	17.1	13.8, 20.9	91	20.0	16.4,23.9
< 1 inch	**Mild**	57	12.5	9.6, 15.9	75	16.4	13.2,20.2
1 – 2 inches	**Moderate**	18	3.9	2.4, 6.2	15	3.3	1.9,5.4
> 2 inches	**Severe**	3	0.7	0.1, 1.9	1	0.2	0.0,1.2
Pain							
	Any	212	46.5	41.8, 51.2	343	75.2	71.0,79.1
	Mild	176§	38.6	34.1, 43.2	261	57.2	52.6,61.8
	Moderate	33	7.2	5.0, 10.0	80	17.5	14.2,21.4
	Severe	3	0.7	0.1, 1.9	2	0.4	0.1,1.6

§ Some participants reported a mild or moderate pain reaction during Days 0-3, but subsequently reported the reaction as moderate or severe during Days 4-7, respectively. Since each participant is counted only once according to the highest severity score reported, the number of participants with mild reactions during Days 0-7 may be lower than the number of participants in the Days 0-3 subcategory.

Menactra injection site: Visits 1 (1st vaccination) and 2 (2nd vaccination)
MTA-11 Table 9 summarizes local adverse events at the Menactra injection site when Menactra given with Vi (Group A, visit 1), or after Vi (Group B, visit 2).

MTA-11: Menactra Local adverse reactions (Days 0-7)

		Group A			Group B		
		Vi + **Menactra,** Then Placebo			Vi + Placebo, Then **Menactra**		
		(Menactra Injection site)			(Menactra Injection site)		
Reaction	**Severity**	**n*/N**	**%†**	**95% CI**	**n*/N**	**%†**	**95% CI**
Redness							
	Any	52/456	11.4	8.6, 14.7	62/439	14.1	11.0, 17.7
< 1 inch	**Mild**	32/456	7.0	4.8, 9.8	43/439	9.8	7.2, 13.0
1 – 2 inches	**Moderate**	16/456	3.5	2.0, 5.6	16/439	3.6	2.1, 5.9
> 2 inches	**Severe**	4/456	0.9	0.2, 2.2	3/439	0.7	0.1, 2.0
Swelling							
	Any	61/456	13.4	10.4, 16.8	50/439	11.4	8.6, 14.7
< 1 inch	**Mild**	44/456	9.6	7.1, 12.7	31/439	7.1	4.8, 9.9
1 – 2 inches	**Moderate**	14/456	3.1	1.7, 5.1	15/439	3.4	1.9, 5.6
> 2 inches	**Severe**	3/456	0.7	0.1, 1.9	4/439	0.9	0.2, 2.3
Induration							
	Any	78/456	17.1	13.8, 20.9	67/439	15.3	12.0, 19.0
< 1 inch	**Mild**	57/456	12.5	9.6, 15.9	46/439	10.5	7.8, 13.7
1 – 2 inches	**Moderate**	18/456	3.9	2.4, 6.2	18/439	4.1	2.4, 6.4
> 2 inches	**Severe**	3/456	0.7	0.1, 1.9	3/439	0.7	0.1, 2.0
Pain							
	Any	212/456	46.5	41.8, 51.2	192/439	43.7	39.0, 48.5
	Mild	176/456§	38.6	34.1, 43.2	140/439	31.9	27.6, 36.5
	Moderate	33/456	7.2	5.0, 10.0	44/439	10.0	7.4, 13.2
	Severe	3/456	0.7	0.1, 1.9	8/439	1.8	0.8, 3.6

*n: Number of participants reporting at least one event in this category.
†%: 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:

MTA-11 Table 11: Systemic adverse reactions after Menactra vaccination (Days 0-7)

		Group A			Group B		
		Vi + Menactra, Then Placebo			Vi + Placebo, **Then Menactra**		
Reaction	**Severity**	**n*/N**	**%†**	**95% CI**	**n*/N**	**%†**	**95% CI**
Fever							
	Any	4/448	0.9	0.2, 2.3	5/434	1.2	0.4, 2.7
38.0ºC-38.9ºC	**Mild**	3/448	0.7	0.1, 1.9	5/434	1.2	0.4, 2.7
39.0ºC-39.9ºC	**Moderate**	1/448	0.2	0.0, 1.2	0/434	0.0	0.0, 0.8
≥ 40.0ºC	**Severe**	0/448	0.0	0.0, 0.8	0/434	0.0	0.0, 0.8

Cont. MTA-11 Table 11: Systemic adverse reactions after Menactra vaccination (Days 0-7)							
		Group A			Group B		
		Vi + Menactra, Then Placebo			Vi + Placebo, Then Menactra		
Reaction	Severity	n*/N	%†	95% CI	n*/N	%†	95% CI
Headache							
	Any	185/456	40.6	36.0, 45.2	143/439	32.6	28.2, 37.2
	Mild	127/456	27.9	23.8, 32.2	104/439	23.7	19.8, 28.0
	Moderate	52/456	11.4	8.6, 14.7	37/439	8.4	6.0, 11.4
	Severe	6/456	1.3	0.5, 2.8	2/439	0.5	0.1, 1.6
Fatigue							
	Any	172/456	37.7	33.3, 42.3	119/439	27.1	23.0, 31.5
	Mild	123/456	27.0	23.0, 31.3	81/439	18.5	14.9, 22.4
	Moderate	41/456	9.0	6.5, 12.0	34/439	7.7	5.4, 10.7
	Severe	8/456	1.8	0.8, 3.4	4/439	0.9	0.2, 2.3
Arthralgia							
	Any	84/455	18.5	15.0, 22.3	51/439	11.6	8.8, 15.0
	Mild	61/455	13.4	10.4, 16.9	33/439	7.5	5.2, 10.4
	Moderate	20/455	4.4	2.7, 6.7	16/439	3.6	2.1, 5.9
	Severe	3/455	0.7	0.1, 1.9	2/439	0.5	0.1, 1.6
Chills							
	Any	30/455	6.6	4.5, 9.3	14/427	3.3	1.8, 5.4
	Mild	22/455	4.8	3.1, 7.2	13/427	3.0	1.6, 5.1
	Moderate	6/455	1.3	0.5, 2.8	1/427	0.2	0.0, 1.3
	Severe	2/455	0.4	0.1, 1.6	0/427	0.0	0.0, 0.9
Anorexia							
	Any	50/456	11.0	8.2, 14.2	38/439	8.7	6.2, 11.7
Skips 1 meal	**Mild**	37/456	8.1	5.8, 11.0	32/ 439	7.3	5.0, 10.1
Skips 2 meals	**Moderate**	10/456	2.2	1.1, 4.0	4/439	0.9	0.2, 2.3
Skips ≥ 3 meals	**Severe**	3/456	0.7	0.1, 1.9	2/439	0.5	0.1, 1.6
Vomiting							
	Any	10/456	2.2	1.1, 4.0	8/439	1.8	0.8, 3.6
1 episode	**Mild**	5/456	1.1	0.4, 2.5	7/439	1.6	0.6, 3.3
2 episodes	**Moderate**	3/456	0.7	0.1, 1.9	0/439	0.0	0.0, 0.8
≥3 episodes	**Severe**	2/456	0.4	0.1, 1.6	1/439	0.2	0.0, 1.3
Diarrhea							
	Any	54/455	11.9	9.0, 15.2	32/439	7.3	5.0, 10.1
1-2 episodes	**Mild**	40/455	8.8	6.4, 11.8	25/439	5.7	3.7, 8.3
3-4 episodes	**Moderate**	13/455	2.9	1.5, 4.8	7/439	1.6	0.6, 3.3
> 5 episodes	**Severe**	1/455	0.2	0.0, 1.2	0/439	0.0	0.0, 0.8
Seizures (Y/N)							
Yes	**Days 0-3**	0/455	0.0	0.0, 0.8	0/439	0.0	0.0, 0.8
Yes	**Days 4-7**	0/455	0.0	0.0, 0.8	0/439	0.0	0.0, 0.8
Yes	**Days 0-7**	0/455	0.0	0.0, 0.8	0/439	0.0	0.0, 0.8
Rash							
Any rash	**Days 0-3**	8/455	1.8	0.8, 3.4	2/439	0.5	0.1, 1.6
Any rash	**Days 4-7**	7/455	1.5	0.6, 3.1	1/439	0.2	0.0, 1.3
Any rash	**Days 0-7**	11/455	2.4	1.2, 4.3	2/439	0.5	0.1, 1.6

*n: Number of participants reporting at least one event in this category.

†%: n/N expressed as a percentage.

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

6.2 Study MTA-12

Title: Immunogenicity and Safety of Tetanus/diphtheria (Td) Vaccine When Administered Concomitantly with an Experimental Tetravalent (A, C, Y, and W-135) Meningococcal Diphtheria Toxoid Conjugate Vaccine in Adolescents in the U.S.

Objectives

- Primary objectives:
  1. To compare the tetanus and diphtheria toxoid booster response, when Td vaccine is co-administered with a saline placebo or with Menactra.
  2. To compare the bactericidal antibody response to serogroups A, C, Y, W135, using baby rabbit complement (SBA-BR), when Menactra is co-administered with Td, to the corresponding antibody response when Menactra is given 28 days after Td vaccination.
- Secondary objectives:
  1. To compare the proportion of participants with antibody levels ≥1.0 IU/mL to tetanus and diphtheria toxoids, when Td vaccine is co-administered with a saline placebo or Menactra.
  2. To compare the geometric mean antibody concentrations to tetanus and diphtheria toxoids, when Td vaccine is co-administered with a saline placebo or Menactra.
  3. To compare the bactericidal antibody titer to serogroups A, C, Y, W135, using baby rabbit complement (SBA-BR), when Menactra is co-administered with Td, to the corresponding antibody response when Menactra is given 28 days after Td vaccination.
- Other objectives:
  - To describe the safety profile for participants in each vaccine group.
  - To compare the post-vaccination SBA-BR geometric mean titer for serogroups A, C, Y and W135, in both vaccine groups of the proposed study, to the corresponding antibody response in Menactra participants in study MTA-02.

Design: The study was a randomized, double blind, multi-center, controlled trial. Participants were randomized in a 1: 1 ratio (Menactra + Td: Td, then Menactra), and were enrolled at eight study centers in the United States.

Vaccine administration

Each group received two injections 28 days apart. Group A received Td + Menactra, then a saline placebo. Group B received Td + saline placebo, followed by Menactra. Participants received all injections intramuscularly.

Tetanus and Diphtheria Toxoids Adsorbed for Adult Use® is a commercially available in the United States. Each 0.5mL dose contains 5Lf of tetanus toxoid, 2Lf of diphtheria toxoid and not more than 0.28mg of aluminum by assay. Tetanus and diphtheria toxoids induce at least 2 units and 0.5 units of antitoxin per mL, respectively, in the guinea pig potency test. The vaccine is formulated as liquid, and after shaking, appears as a turbid, whitish gray suspension. Td vaccine was supplied in single dose vials.

Buffered Sterile Normal Saline (0.9% NaCl) was utilized as the placebo.

Primary Endpoints:

- The proportion of participants who have a booster response to tetanus and diphtheria antigens
- The proportion of participants with at least a 4-fold increase in SBA-BR antibody titer to each serogroup

Secondary endpoints:

- ?? The proportion of participants with anti-diphtheria and anti-tetanus antibody levels ≥ 1.0 IU/ml
- ?? Anti-diphtheria and anti-tetanus geometric mean antibody concentrations among these recipients
- ?? SBA-BR geometric mean antibody titer to each meningococcal serogroup

Surveillance

Monitored parameters:

Safety: Study participants were monitored for immediate reactions 30 minutes after 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), which were assessed after each vaccination. These events were recorded daily on a diary card, and also collected by study personnel through telephone interview eight days after each 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 each vaccination. Serious adverse events were reported and recorded during the entire duration of the study.

Efficacy (Immunogenicity):

Serum samples were obtained pre- and 28 days after each vaccination.

Anti-Meningococcal Antibody

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.

Anti-diphtheria Antibody

Anti-diphtheria antibody response, reported in International Units/mL (IU/mL), was measured by the ability of the test sera to ---------- ---------- ---------- The assay is calibrated using a WHO reference serum and to determine the limits of detection. The minimum detectable antitoxin level of the reference serum, and the starting dilution of the test sera, is --------IU/mL.

Anti-tetanus Antibody

Anti-tetanus IgG antibody levels were measured by an ---------- Enzyme Linked Immunosorbent Assay (ELISA). The antibody concentration was calculated by comparison to an international human reference (WHO Lot TE-3) with assigned unitage by a ----------method. Results are reported as International Units per milliliter (IU/mL). The minimum level of quantitation for this assay is ------ IU/mL.

Statistical plan

Primary Hypotheses:

Primary Hypothesis #1:

To demonstrate that 28 days following concomitant vaccination with Td and Menactra, the proportion of participants who have a booster response to tetanus and diphtheria antigens is non-inferior to the same parameter in the group given Td together with a saline placebo, followed by Menactra 28 days later. The definition of a post-vaccination booster response to tetanus and diphtheria antigens is based on the baseline pre-vaccination level. For participants with a baseline anti-diphtheria antibody level = 1.28 IU/mL and/or an anti-tetanus antibody level= 5.3 IU/mL, a booster response is at least a 4-fold increase in baseline level to each respective antigen. For participants with a baseline anti-diphtheria antibody level

>1.28 IU/mL and/or an anti-tetanus antibody level >5.3 IU/mL, at least a 2-fold increase in antibody level to each respective antigen is needed.

This hypothesis would be supported by the data if the upper bound of the two-sided 95% CI of $p_{Td + placebo} - p_{Td + Menactra} < 0.1$, where p is the proportion of participants with acceptable increases in antibody level to diphtheria and tetanus, as stated in the preceding paragraph, in the group given a staggered and concomitant dosing regimen of Td and Menactra, respectively. The sample size provided 99.6% and 99.9% power to achieve the primary hypothesis for tetanus and diphtheria, respectively. Testing of the primary hypothesis was conducted at the one-sided 0.025 significance level.

Primary Hypothesis #2:
To demonstrate that 28 days post Menactra vaccination, the proportion of participants with at least a 4-fold increase in SBA-BR antibody titer to serogroups A, C, Y, and W-135 in the Td + Menactra group is non-inferior to the same parameter in the group given Td together with a saline placebo, followed by Menactra 28 days later.

This hypothesis would be supported by the data if the upper limit of the two-sided 95% confidence limit $P_{Menactra} - P_{Td+Menactra} < 0.1$, where p is the proportions of participants with at least a 4-fold rise in SBA-BR antibody to meningococcal serogroups A, C, Y, and W-135, in the Td + placebo and Td + Menactra groups, respectively. The sample size provided 88.7% power, overall, to achieve the primary hypothesis for each serogroup. Testing of the primary hypothesis was conducted at the one-sided 0.025 significance level. The primary analyses were based on data generated from the per-protocol population.

Secondary Hypotheses:
Secondary Hypothesis #1:
To demonstrate that 28 days following concomitant vaccination with Td vaccine and Menactra, the proportion of participants with anti-diphtheria and anti-tetanus antibody levels $\geq$ 1.0 IU/ml is non-inferior to the same parameter in the group given Td together with a saline placebo, followed by Menactra 28 days later.

This hypothesis would be supported by the data if the upper bound of the two-sided 95% CI of $p_{Td + placebo} - p_{Td + Menactra} < 0.1$ for both antigens, where p is the proportion of participants with antibody titer $\geq$ 1.0 IU/ml to diphtheria and tetanus in the groups given [Td + placebo, then Menactra] and [Td + Menactra], respectively.

Secondary Hypothesis #2:
To demonstrate that 28 days following concomitant vaccination with Td vaccine and Menactra, the anti-diphtheria and anti-tetanus geometric mean antibody concentrations among these recipients is non-inferior to the same parameter in the group given Td together with a saline placebo, followed by Menactra 28 days later.

This hypothesis would be supported by the data if the upper bound of the two-sided 95% CI of the ratio $GMT_{Td + Placebo} / GMT_{Td + Menactra} < 2$.

Secondary Hypothesis #3:
To demonstrate that 28 days following vaccination with Menactra, the SBA-BR geometric mean antibody titer for serogroups A, C, Y, and W-135 in the group receiving a staggered dosing regimen of Menactra and Td vaccines is non-inferior to the same parameter in the group receiving the two vaccines concomitantly.

This hypothesis would be supported by the data if the upper bound of the two-sided 95% CI of the ratio $GMT_{Menactra} / GMT_{Td + Menactra} < 2$, where $GMT_{Menactra}$ and $GMT_{Td + Menactra}$ are the proportion of participants with at least a 4-fold rise in SBA-BR antibody to meningococcal serogroups A, C, Y, and W-

135, in the [Td + placebo] and [Td + Menactra] groups, respectively. Analyses of the secondary points were performed on both per-protocol and intent-to-treat populations.

Per-protocol population for immunogenicity:
The per-protocol population included all eligible participants who received the assigned vaccine at visits 1 & 2, 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 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.

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, initial designation of each rash as severe emphasized to the investigator that additional descriptive information regarding the occurrence and description of the rash was needed.

Results
The group given Td co-administered with Menactra, is designated Group A. The group receiving a staggered vaccination schedule [Td + saline placebo, then Menactra 28 days later] is designated Group B. A total of 1021 (Group A n=509, Group B n= 512) adults were enrolled, and 990 (Group A n=492, Group B n= 498) individuals completed the study. The intent-to-treat population for safety included all enrolled participants (n= 1021). The per protocol population for immunogenicity included 469 Group A and 478 Group B 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 (89.8%), but also included African American (4.8%), Hispanic (2.6%), Asian populations (0.5%) and individuals with mixed racial background (2.3%).

Immunogenicity
Four-fold or greater increases in SBA-BR titer 28 days after Menactra vaccination:
The proportion (expressed as a percentage) of participants who received Td prior to Menactra, and achieved a ≥four-fold increase in SBA-BR titer post-vaccination was 90.6% for serogroup A, 82.4% for serogroup C, 65.1% for serogroup Y and 87.7% for serogroup W135. In the same order, the proportion of participants in the concomitant vaccine group who achieved the stated criteria was 90.1%, 91.9%, 85.8% and 96.3%, respectively.

MTA-12: Number and Proportion of Participants 11-17 Years Old with ≥ 4-fold Increase in SBA-BR Antibody Titer on Day 28, compared to Baseline

Serogroup	Td+ Placebo, Then Menactra		Td + Menactra Then Placebo		Difference ($p_{Td + placebo}$ - $p_{Td + Menactra}$)	Upper Limit of the 2-sided 95% CI for the Difference§
	N=465		N=478			
	n*	$p_{Menactra}$	n*	$p_{Td + Menactra}$		
A	433	0.906	419	0.901	0.005	0.043
C	394	0.824	424	0.912	-0.088	-0.045
Y	**311**	**0.651**	**399**	**0.858**	**-0.207**	**-0.154**
W-135	419	0.877	448	0.963	-0.087	-0.053

* n: number of participants with a booster response on 28 days post-vaccination. N: total number of participants with valid serology results on Day 28.
§ CI: Confidence interval.

Proportions with diphtheria and tetanus antibody levels >1.0IU/ml or greater:

Diphtheria: The upper limit of the 2-sided 95% CI for the difference in two proportions was 0.001 (0.10%).

Tetanus: The upper limit of the 2-sided 95% CI for the difference in two proportions was 0.008 (0.80%).

MTA-12: Number and Proportion of Participants 11-17 Years Old with Diphtheria and Tetanus Antibody Levels ≥1.0 IU/ml Post-vaccination

	Td + Placebo, Then Menactra		Td + Menactra Then Placebo		Difference ($p_{Td + placebo}$ - $p_{Td + Menactra}$)	Upper Limit of the 2-sided 95% CI for the Difference§
	n/N*	$p_{Td + Placebo}$	n/N*	$p_{Td + Menactra}$		
Diphtheria	470/473	0.994	465/465	1.0	-0.006	0.001
Tetanus	470/477	0.985	460/464	0.991	-0.006	0.008

* n: number of participants with a booster response on 28 days post-vaccination. N: total number of participants with valid serology results on Day 28.

§ CI: Confidence interval.

Diphtheria and Tetanus GMT:

The diphtheria GMT prior to vaccination was 0.4 IU/ml in each group. Twenty-eight days following Td vaccination, the GMT increased to 8.35 IU/ml in the group given a staggered vaccine regimen, and 120.88 IU/ml in the group given the vaccines concomitantly (MTA-12 Table 4).

MTA-12: Comparison of Diphtheria and Tetanus GMT (IU/ml) Post-vaccination

	Td+ Placebo, Then Menactra			Td + Menactra Then Placebo			Ratio of $GMT_{Td + Placebo}$ / $GMT_{Td + Menactra}$	Upper Limit of the 2-sided 95% CI§ for the GMT Ratio
	N	GMT	95% CI	N	GMT	95% CI		
Diphtheria	473	8.4	7.6, 9.2	465	120.9	104.6, 139.8	0.07	0.08
Tetanus	477	13.6	12.7, 14.4	464	11.5	10.8, 12.2	1.18	1.29

§ CI: Confidence interval.

Baseline SBA-BR GMT:

At baseline, the proportion of control group recipients with a SBA-BR titer ≥1:8 to serogroups A, C, Y and W-135 was 89% [425/478], 68% [325/478], 81% [385/478], and 55% [265/478], respectively. Similar distributions of pre-vaccination SBA-BR titer were observed in the concomitant vaccine group. The distribution of baseline bactericidal antibody titer.

SBA-BR GMT 28 days after Menactra vaccination:

MTA-12: Comparison of SBA-BR GMT to Meningococcal Serogroups A, C, Y, W135 Post-vaccination

Serogroup	Td+ Placebo, Then Menactra	Td + Menactra Then Placebo	Ratio of $GMT_{Menactra}$ / $GMT_{Td + Menactra}$	Limits of the 2-sided 95% CI for the GMT Ratio
	N=466	N=478		
	GMT	GMT		
A	10391.4	11312.8	0.92	0.8, 1.1
C	2136.0	5059.3	0.42	0.3, 0.5
Y	1331.3	3390.9	0.39	0.3, 0.5
W-135	1339.1	4194.7	0.32	0.3, 0.4

§ CI: Confidence interval.

Seroconversion

The 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 after vaccination. Recipients in both groups, with SBA-BR antibody titer less than 1:8 pre-vaccination, achieved this criterion for serogroup A. For serogroup C, seroconversion was observed in 96.7% [148/153] and 99.3% [149/150] of Group B and A recipients, respectively. For the remaining serogroups, of those participants who received a staggered vaccine regimen (Group B), 92.5% [86/93] and 96.7% [206/213] responded with a ≥4-fold antibody rise to serogroups Y and W135, respectively, compared with 97.0% [97/100] and 99.5% [203/204] of individuals who received the vaccines concomitantly.

Safety

Local reactions following first vaccination:

The following table presents local adverse reactions, at the Menactra and Vi injection sites, in the same participant:

MTA-12: Local adverse reactions after the First Vaccination (Days 0-7):
Td (Group A), Menactra (Group A) Injection sites

		Group A			**Group A**		
		Td + **Menactra,** Then Placebo			**Td** + Menactra, Then Placebo		
		(Menactra Injection site)			**(Td Injection site)**		
Reaction	**Severity**	**n*/N**	**%†**	**95% CI**	**n*/N**	**%†**	**95% CI**
Redness							
	Any	61/505	12.1	9.4, 15.2	73/505	14.5	11.5, 17.8
< 1 inch	**Mild**	52/505	10.3	7.8, 13.3	58/505	11.5	8.8, 14.6
1 – 2 inches	**Moderate**	3/505	0.6	0.1, 1.7	12/505	2.4	1.2, 4.1
> 2 inches	**Severe**	6/505	1.2	0.4, 2.6	3/505	0.6	0.1, 1.7
Swelling							
	Any	59/505	11.7	9.0, 14.8	83/505	16.4	13.3, 20.0
< 1 inch	**Mild**	47/505	9.3	6.9, 12.2	63/505	12.5	9.7, 15.7
1 – 2 inches	**Moderate**	9/505	1.8	0.8, 3.4	19/505	3.8	2.3, 5.8
> 2 inches	**Severe**	3/505	0.6	0.1, 1.7	1/505	0.2	0.0, 1.1
Induration							
	Any	86/505	17.0	13.9, 20.6	105/505	20.8	17.3, 24.6
< 1 inch	**Mild**	68/505	13.5	10.6, 16.8	75/505	14.9	11.9, 18.3
1 – 2 inches	**Moderate**	13/505	2.6	1.4, 4.4	27/505	5.3	3.6, 7.7
> 2 inches	**Severe**	5/505	1.0	0.3, 2.3	3/505	0.6	0.1, 1.7
Pain							
	Any	267/505	52.9	48.4, 57.3	358/505	70.9	66.7, 74.8
	Mild	§213/505	42.2	37.8, 46.6	244/505	48.3	43.9, 52.8
	Moderate	54/505	10.7	8.1, 13.7	113/505	22.4	18.8, 26.3
	Severe	0/505	0.0	0.0, 0.7	1/505	0.2	0.0, 1.1

*n: Number of participants reporting at least one event in this category.

†%: n/N expressed as a percentage.

§ Some participants reported a mild or moderate pain reaction during Days 0-3, but subsequently reported the reaction as moderate or severe during Days 4-7, respectively. Since each participant is counted only once according to the highest severity score reported, the number of participants with mild reactions during Days 0-7 may be lower than the number of participants in the Days 0-3 subcategory.

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

Menactra injection site: Visits 1 (1st vaccination) and 2 (2nd vaccination)

MTA-12: Menactra local adverse reactions (Days 0-7)										
		Group A (N= 505)			Group B (N= 505)			MTA-04		
		Td + **Menactra,** Then Placebo			Td + Placebo, Then **Menactra**			**Menactra**		
								N= 2264		
		Menactra Injection site			**Menactra Injection site**			**Menactra Injection site**		
Reaction	**Severity**	**n**	**%†**	**95% CI**	**n**	**%†**	**95% CI**	**n***	**%†**	**95% CI**
Redness										
	Any	61	12.1	9.4, 15.2	56	11.1	8.5, 14.2	247	10.9	9.65, 12.27
< 1 inch	**Mild**	52	10.3	7.8, 13.3	40	7.9	5.7, 10.6	197	8.7	7.57, 9.94
1 – 2 inches	**Moderate**	3	0.6	0.1, 1.7	11	2.2	1.1, 3.9	37	1.6	1.15, 2.25
> 2 inches	**Severe**	6	1.2	0.4, 2.6	5	1.0	0.3, 2.3	13	0.6	0.31, 0.98
Swelling										
	Any	59	11.7	9.0, 14.8	66	13.1	10.3, 16.3	245	10.8	9.57, 12.17
< 1 inch	**Mild**	47	9.3	6.9, 12.2	44	8.7	6.4, 11.5	191	8.4	7.32, 9.66
1 – 2 inches	**Moderate**	9	1.8	0.8, 3.4	15	3.0	1.7, 4.9	43	1.9	1.38, 2.55
> 2 inches	**Severe**	3	0.6	0.1, 1.7	7	1.4	0.6, 2.8	11	0.5	0.24, 0.87
Induration										
	Any	86	17.0	13.9, 20.6	78	15.4	12.4, 18.9	355	15.7	14.21, 17.24
< 1 inch	**Mild**	68	13.5	10.6, 16.8	61	12.1	9.4, 15.2	292	12.9	11.54, 14.35
1 – 2 inches	**Moderate**	13	2.6	1.4, 4.4	12	2.4	1.2, 4.1	56	2.5	1.87, 3.20
> 2 inches	**Severe**	5	1.0	0.3, 2.3	5	1.0	0.3, 2.3	7	0.3	0.12, 0.64
Pain										
	Any	267	52.9	48.4, 57.3	270	53.5	49.0, 57.9	1340	59.2	57.13, 61.22
	Mild	213	42.2	37.8, 46.6	198	39.2	34.9, 43.6	1045	46.2	44.09, 48.24
	Moderate	54	10.7	8.1, 13.7	68	13.5	10.6, 16.8	289	12.8	11.42, 14.21
	Severe	0	0.0	0.0, 0.7	4	0.8	0.2, 2.0	6	0.3	0.10, 0.58

*n: Number of participants reporting at least one event in this category.
†%: 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
Study MTA-04 enrolled participants 11-18 years old.

Systemic reactions:

MTA-12: Systemic adverse reactions (Days 0-7)							
		Group A			Group B		
		Td + Menactra, Then Placebo			Td + Placebo, Then **Menactra**		
Reaction	**Severity**	**n*/N**	**%†**	**95% CI**	**n*/N**	**%†**	**95% CI**
Fever							
	Any	25/503	5.0	3.2, 7.2	11/505	2.2	1.1, 3.9
38.0ºC-38.9ºC	**Mild**	19/503	3.8	2.3, 5.8	10/505	2.0	1.0, 3.6
39.0ºC-39.9ºC	**Moderate**	5/503	1.0	0.3, 2.3	1/505	0.2	0.0, 1.1
≥ 40.0ºC	**Severe**	1/503	0.2	0.0, 1.1	0/505	0.0	0.0, 0.7
Headache							
	Any	180/505	35.6	31.5, 40.0	110/505	21.8	18.3, 25.6
	Mild	116/505	23.0	19.4, 26.9	79/505	15.6	12.6, 19.1
	Moderate	54/505	10.7	8.1, 13.7	28/505	5.5	3.7, 7.9
	Severe	10/505	2.0	1.0, 3.6	3/505	0.6	0.1, 1.7

Cont. MTA-12: Systemic adverse reactions (Days 0-7)							
		Group A			**Group B**		
		Td + Menactra, Then Placebo			Td + Placebo, Then **Menactra**		
Reaction	**Severity**	**n*/N**	**% †**	**95% CI**	**n*/N**	**% †**	**95% CI**
Malaise							
	Any	119/505	23.6	19.9, 27.5	61/505	12.1	9.4, 15.2
	Mild	72/505	14.3	11.3, 17.6	35/505	6.9	4.9, 9.5
	Moderate	36/505	7.1	5.0, 9.7	21/505	4.2	2.6, 6.3
	Severe	11/505	2.2	1.1, 3.9	5/505	1.0	0.3, 2.3
Arthralgia							
	Any	127/505	25.1	21.4, 29.2	61/505	12.1	9.4, 15.2
	Mild	94/505	18.6	15.3, 22.3	45/505	8.9	6.6, 11.7
	Moderate	29/505	5.7	3.9, 8.1	15/505	3.0	1.7, 4.9
	Severe	4/505	0.8	0.2, 2.0	1/505	0.2	0.0, 1.1
Chills							
	Any	56/505	11.1	8.5, 14.2	18/505	3.6	2.1, 5.6
	Mild	35/505	6.9	4.9, 9.5	16/505	3.2	1.8, 5.1
	Moderate	18/505	3.6	2.1, 5.6	2/505	0.4	0.0, 1.4
	Severe	3/505	0.6	0.1, 1.7	0/505	0.0	0.0, 0.7
Anorexia							
	Any	64/505	12.7	9.9, 15.9	22/505	4.4	2.7, 6.5
Skips 1 meal	**Mild**	43/505	8.5	6.2, 11.3	15/505	3.0	1.7, 4.9
Skips 2 meals	**Moderate**	16/505	3.2	1.8, 5.1	5/505	1.0	0.3, 2.3
Skips ≥ 3 meals	**Severe**	5/505	1.0	0.3, 2.3	2/505	0.4	0.0, 1.4
Vomiting							
	Any	23/505	4.6	2.9, 6.8	7/505	1.4	0.6, 2.8
1 episode	**Mild**	17/505	3.4	2.0, 5.3	5/505	1.0	0.3, 2.3
2 episodes	**Moderate**	6/505	1.2	0.4, 2.6	1/505	0.2	0.0, 1.1
≥3 episodes	**Severe**	0/505	0.0	0.0, 0.7	1/505	0.2	0.0, 1.1
Diarrhea							
	Any	45/505	8.9	6.6, 11.7	19/505	3.8	2.3, 5.8
1-2 episodes	**Mild**	39/505	7.7	5.5, 10.4	15/505	3.0	1.7, 4.9
3-4 episodes	**Moderate**	5/505	1.0	0.3, 2.3	4/505	0.8	0.2, 2.0
≥ 5 episodes	**Severe**	1/505	0.2	0.0, 1.1	0/505	0.0	0.0, 0.7
Seizures (Y/N)							
Yes	**Days 0-3**	0/505	0.0	0.0, 0.7	0/505	0.0	0.0, 0.7
Yes	**Days 4-7**	0/505	0.0	0.0, 0.7	0/505	0.0	0.0, 0.7
Yes	**Days 0-7**	0/505	0.0	0.0, 0.7	0/505	0.0	0.0, 0.7
Rash							
Any rash	**Days 0-3**	4/505	0.8	0.2, 2.0	4/505	0.8	0.2, 2.0
Any rash	**Days 4-7**	7/505	1.4	0.6, 2.8	4/505	0.8	0.2, 2.0
Any rash	**Days 0-7**	9/505	1.8	0.8, 3.4	7/505	1.4	0.6, 2.8

*n: Number of participants reporting at least one event in this category.
†%: n/N expressed as a percentage.
Headache, chills, arthralgia, fatigue, malaise: 0= none, 1= aware, easily tolerated, 2= interferes with usual activities, 3= disabling

7.0 Lot Consistency

Title: A Trial of the Lot Consistency of an Experimental Tetravalent (A, C, Y, and W-135) Meningococcal Diphtheria Toxoid Conjugate Vaccine Among Healthy U.S. Adults

(Please see section 6.4 for synopsis of study design. This study contained both safety and immunogenicity primary objectives.)

Objectives

- Primary objective:
  To assess the consistency of the immune response from three manufactured lots of Menactra, as measured by the bactericidal antibody response to serogroups A, C, Y, W135, using baby rabbit complement (SBA-BR) in the assay.
- Other objectives:
  - To describe and compare the SBA-BR response to each serogroup pre- and 28 days post-vaccination for all participants who receive Menactra.
  - To describe and compare the proportion of participants who achieve seroconversion 28 days following vaccination with any of the three Menactra vaccine lots.

Primary Endpoint:

- The immune responses to the three consistency lots of Menactra, as measured by the SBA-BR geometric mean titer (GMT)

Surveillance (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.

Statistical plan

Primary Hypothesis:

To demonstrate that 28 days after vaccination, the immune responses to the three consistency lots of Menactra, as measured by the SBA-BR geometric mean titer (GMT), are equivalent for each of the four serogroups.

This hypothesis will be supported by the data if the upper limit of the two-sided 90% confidence interval of the difference between the maximum and the minimum treatment effect among the three lot responses is $< \log_2 (1.5)$ for each of the four serogroups. Planned enrollment of 1599 participants for the lot consistency evaluation, with resultant 1400 evaluable study subjects, provided 99.9% power, overall, to achieve the primary hypothesis for serogroups A, C, Y and W135. The per-protocol population for immunogenicity was used for the primary analysis.

Results

MTA-14: SBA-BR Geometric Mean Titer Pre- and 28 days Post-vaccination							
		Menactra		Menactra		Menactra	
		Lot 1		Lot 2		Lot 3	
		N= 496 (pre)/ 495 (post)		N= 486		N= 499	
Serogroup	Timepoint	SBA-BR GMT	95% CI	SBA-BR GMT	95% CI	SBA-BR GMT	95% CI
A	Day 0	239.1	191.1, 299.0	271.4	217.9, 338.1	248.6	198.7, 311.2
	Day 28	8169.1	7363.5, 9062.8	8215.4	7388.3, 9135.1	6679.0	5976.3, 7464.3
C	Day 0	72.6	58.6, 89.9	57.3	46.5, 70.7	79.3	63.7, 98.6
	Day 28	3867.5	3299.4, 4533.4	4154.8	3621.4, 4766.9	3216.6	2743.1, 3771.7
Y	Day 0	243.8	201.6, 294.9	184.7	151.1, 225.7	208.4	171.0, 254.1
	Day 28	2898.3	2541.2, 3305.7	2477.2	2150.2, 2842.6	3805.3	3331.6, 4346.3
W-135	Day 0	47.4	38.8, 57.8	48.5	39.8, 59.1	44.5	36.7, 53.9
	Day 28	2030.9	1742.8, 2366.5	2573.0	2199.1, 3010.5	2456.7	2136.1, 2825.4

MTA-14: Number and Percentage of Participants 18-55 Years Old Achieving a ≥ Four-fold Increase in SBA-BR Antibody Titer, with 95%CI									
	Menactra			Menactra			Menactra		
	Lot 1			Lot 2			Lot 3		
Serogroup	N= 495			N= 486			N= 499		
	n*	$P_{Menactra}$†	95% CI	n*	$P_{Menactra}$†	95% CI	n*	$P_{Menactra}$†	95% CI
A	421	85.1%	81.6, 88.1	415	85.4%	81.9, 88.4	407	81.6%	77.9, 84.9
C	425	85.9%	82.5, 88.8	435	89.5%	86.4, 92.1	415	83.2%	79.6, 86.3
Y	371	74.9%	70.9, 78.7	348	71.6%	67.4, 75.6	402	80.6%	76.8, 83.9
W-135	426	86.1%	82.7, 89.0	428	88.1%	84.9, 90.8	458	91.8%	89.0, 94.0

*n: number of participants with = 4-fold rise SBA-BR titer from baseline. N: total number of participants with valid serology data.
† $p_{Menomune®}$: percentage of Menomune® participants with a =4-fold rise in SBA-BR titer post-vaccination, compared with baseline.
‡ $p_{Menactra}$: percentage of Menactra participants with a = 4-fold rise in SBA-BR titer post-vaccination compared with baseline.
§ CI: Confidence interval.

Seroconversion 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 after vaccination. All Menactra recipients with SBA-BR antibody titer less than 1:8 pre-vaccination achieved this criterion for serogroup A. The minimum proportion of Menactra participants who achieve seroconversion for serogroups C, Y and W135 was 95.7% [133/139, lot 1], 92.9% [79/85, lot 2] and 94.6% [158/167, lot 2]. The maximum proportion of Menactra participants who achieve seroconversion, in the same order, was 100.0% [144/144, lot 2], 96.6% [85/88, lot 3] and 97.6% [165/169, lot 3].

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