Study MTA-14: 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

7.1.5.6 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.
- Secondary objectives:
  - ✓ To compare the safety profile of each Menactra vaccine lot
  - ✓ To assess the consistency of the immune response from three Menactra lots, as measured by the proportion of participants with at least a 4-fold increase in SBA-BR antibody from baseline
  - ✓ 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
  - ✓ 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.
  - ✓ To describe the SBA-BR findings for serogroups A, C, Y and W-135 for a subset of Menactra and Menomune® recipients at the 6-month post-vaccination timepoint.

7.1.5.7 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®.

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.

Study Period: June 03, 2002 to Mar 02, 2003

7.1.5.8 Protocol

7.1.5.8.1 Population

The study was conducted at twenty-four study centers in the United States.

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

Exclusion criteria:
- Serious chronic disease (i.e. cardiac, renal, neurologic, metabolic, rheumatologic etc.)
- Known or suspected impairment immunologic function

- History of documented invasive meningococcal disease or previous meningococcal vaccination
- Receipt of immune globulin or other blood products within the previous 3 months, injected or oral corticosteroids within 6 weeks prior to the administration of the study vaccine
- Administration of a vaccine other than the study vaccine within 28 days of enrollment
- Antibiotic therapy within 72 hours prior to visits 1 or 2
- Known or suspected hypersensitivity to any vaccine component
- Enrolled in another clinical trial
- Any condition which, in the opinion of the investigator, would pose a health risk to the participant
- Unable to comply with scheduled visits or study procedures
- For females, a positive or equivocal urine pregnancy test result on the day of vaccination
- Breastfeeding

Reasons for deferring vaccination

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

7.1.5.8.2 Vaccine administration

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

7.1.5.8.3 Endpoints

Primary Endpoint:

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

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 with at least a 4-fold rise in SBA-BR antibody titer from baseline, are equivalent for each of the four serogroups.
- 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.

7.1.5.8.4 Surveillance

Monitored parameters:

Surveillance for safety and immunogenicity parameters was obtained in the same manner as described in study MTA-09. Since Menomune® participants were enrolled for safety comparisons, sera were not obtained for these participants.

7.1.5.8.5 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 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.

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 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. This analysis was based on data generated from the intent-to-treat population for safety.

Secondary Hypothesis #2:

To demonstrate that 28 days after vaccination, the immune responses from the three lots of Menactra, as measured by the proportion of participants with at least a 4-fold rise in SBA-BR antibody titer from baseline, are equivalent for each of the four serogroups.

This hypothesis would be supported if the upper limit of the 2-sided 95% CI of the difference between the maximum and minimum proportion of participants among the three lot responses is less than 0.1. Analyses of the secondary points were performed on both per-protocol and intent-to-treat populations for immunogenicity.

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 if the upper limit of the 2-sided 95% CI of the difference in two proportions is less than 0.1. This analysis was based on data generated from the intent-to-treat population for safety.

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.

Observational Immunogencity analyses:

An observational objective was added during the trial, which included analysis of functional antibody responses from sera obtained 6-months post-vaccination, in a subset of Menactra and Menomune® recipients. Measurement of SBA-BR geometric mean antibody titer for each serogroup is anticipated, and the results compared to historical controls. These results were not included in the license application, but anticipated to be submitted as a separate supplemental immunogenicity report.

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 immunogenicity:

The intent-to-treat population consisted of all enrolled participants who received one dose of vaccine underwent at least one blood draw. Analyses were performed according to the vaccine received.

For analysis purposes, if the SBA-BR antibody titer to any serogroup was reported below the limit of

detection, the antibody titer assigned was a value equal to the limit of detection. ITT analyses for the primary and secondary endpoint were considered exploratory. These results were not included in the license application, but anticipated to be submitted as an appendix to the final study report.

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.

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

7.1.5.9 Results

7.1.5.9.1 Population

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.

Safety population:
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). For the Menomune® safety comparison, the intent-to-treat population for safety included 1144 participants (Menactra n= 686, Menomune® n= 458).

One hundred fifty-two participants (Menactra lot 1 n= 36, lot 2 n= 48, lot 3 n= 36; Menomune® n= 32) were not available for the safety assessment 6-months after vaccination, due to voluntary withdrawal, non-compliance with study procedures, or lost-to-follow-up. Two participants (one Menactra [lot 3], one Menomune®) died for reasons unrelated to vaccination, which are described in the serious adverse event section.

Immunogenicity population:
Two hundred Menactra participants (lot 1 n= 68, lot 2 n=67, lot 3 n= 65) were noted to have a protocol violation. Seventy-two participants were excluded from the per-protocol population for reasons such as ineligibility (e.g. prior receipt of a non-study vaccine, antibiotic use within 72 hours prior to enrollment), non-compliance with study procedures, visits outside the scheduled interval, or other (e.g. sera misplaced or inadvertently discarded). The remaining participants with at least one protocol violation were considered evaluable for the per-protocol analysis, since the violation related to safety data collection, rather than serologic data collection (MTA-14 Table 1).

Thirty-two Menactra participants (lot 1 n= 7, lot 2 n= 15, lot 3 n= 7), while not listed for protocol violations, were excluded from the per-protocol population for reasons stated in MTA-14 Table 1 below. A randomization error occurred for one Menactra recipient was assigned to receive lot 3, but instead, received lot 2.

MTA-14 Table 1: Participant disposition for immunogenicity analyses

	Menactra Lot 1	Menactra Lot 2	Menactra Lot 3
All randomized	527 (100.0%)	528 (100.0%)	527 (100.0%)
Received vaccine, but no pre-or post sera drawn	1 (0.2%)	1 (0.2%)	1 (0.2%)
ITT population for immunogenicity	526 (99.8)	527 (99.8%)	526 (99.8%)
I. Any protocol violation	68 (12.9%)	67 (12.7%)	65 (12.3%)
· Any protocol violation, but participant included in PP population	44 (8.3%)	40 (7.6%)	44 (8.3%)
· Excluded due to protocol violation	24 (4.6%)	27 (5.1%)	21 (4.0%)

II. Participants excluded from PP population for immunogenicity	31 (5.9%)	42 (7.9%)	28 (5.3%)
· Participant excluded due to protocol violation	24 (4.6%)	27 (5.1%)	21 (4.0%)
· Not listed as protocol violation, but participant excluded from PP population	7 (1.3%)	15 (2.8%)	7 (1.3%)
Visit for blood draw outside window	2	2	1
Visit, but blood sample not obtained	5	13	6
III. PP population for immunogenicity	496 (94.1%)	486 (92.0%)	499 (94.7%)

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 (85.6%), but also included African American (6.3%), Hispanic (5.0%), Asian populations (1.9%) and individuals with mixed racial background (1.2%).

7.1.5.9.2 Immunogenicity

Baseline SBA-BR geometric mean titer:

MTA-14 Table 2: Number and Percentage of Participants 18-55 Years Old With Baseline SBA-BR titer ≥1:8

Serogroup	Menactra Lot 1 N= 496 n*	%	Menactra Lot 2 N= 486 n*	%	Menactra Lot 3 N= 499 n*	%
A	402	81%	399	82%	400	80%
C	357	72%	342	70%	368	74%
Y	423	85%	401	82%	411	82%
W-135	320	64%	319	66%	330	66%

* n: number of participants with SBA-BR titer ≥1:8 prior to vaccination. N: total number of participants with valid serology data.

SBA-BR geometric antibody responses post-vaccination to serogroups C and Y were variable. The SBA-BR GMT to serogroup C, for each of the three Menactra groups, respectively, was 3867.5, 4154.8 and 3216.6 (MTA-14 Table 3). The SBA-BR GMT to serogroup Y, for each of the three Menactra groups, respectively, was 2898.3, 2477.2 and 3805.3. The mean antibody rise to serogroups Y and A was lower relative to that observed for serogroups C and W135, due to higher pre-existing baseline titer.

MTA-14 Table 3: SBA-BR Geometric Mean Titer Pre- and 28 days Post-vaccination

Serogroup	Timepoint	Menactra Lot 1 N=496 (pre)/ 495 (post) SBA-BR GMT	95% CI	Menactra Lot 2 N= 486 SBA-BR GMT	95% CI
A	Day 0	239.1	191.14, 298.98	271.4	217.88, 338.11
	Day 28	8169.1	7363.52, 9062.79	8215.4	7388.30, 9135.10
C	Day 0	72.6	58.60, 89.90	57.3	46.48, 70.74
	Day 28	3867.5	3299.38, 4533.35	4154.8	3621.36, 4766.90
Y	Day 0	243.8	201.55, 294.86	184.7	151.09, 225.71
	Day 28	2898.3	2541.15, 3305.74	2477.2	2150.16, 2842.57
W-135	Day 0	47.4	38.83, 57.83	48.5	39.82, 59.14
	Day 28	2030.9	1742.81, 2366.53	2573.0	2199.05, 3010.47

Cont. MTA-14 Table 3: SBA-BR Geometric Mean Titer Pre- and 28 days Post-vaccination			
		Menactra Lot 3 N= 490	
Serogroup	Timepoint	SBA-BR GMT	95% CI
A	Day 0	248.6	198.67, 311.17
	Day 28	6679.0	5976.31, 7464.26
C	Day 0	79.3	63.71, 98.61
	Day 28	3216.6	2743.10, 3771.74
Y	Day 0	208.4	170.97, 254.09
	Day 28	3805.3	3331.60, 4346.31
W-135	Day 0	44.5	36.71, 53.89
	Day 28	2456.7	2136.14, 2825.44

N: total number of participants with valid serology data.

Primary hypothesis testing:

MTA-14 Table 4 represents a reanalysis of the primary hypothesis, which excluded nine additional participants with protocol violations (n= 3 per lot). The maximum and minimum treatment effect, using the $\log_2$ SBA-BR response at Day 28, was estimated and adjusted for baseline differences. The difference in treatment effect (max-min) was 0.304, 0.446, 0.587, and 0.326, for serogroups A, C, Y and W135, respectively. The antibody response to the 3 Menactra lots were considered to be consistent if the upper limit of the 90% CI for the antilog$_2$ of the difference in treatment effect, was less than 1.5 for each serogroup. This criterion was met for serogroups A (1.397) and W135 (1.483), but not for serogroups C (1.624) and Y (1.745). Analysis of the intent-to-treat population resulted in same conclusions.

MTA-14 Table 4: Primary Hypothesis: Treatment Effect (Lots #1-3) on the SBA-BR Response Post-vaccination, Adjusted by Baseline Covariate						
	Serum Bactericidal Titer-BR					
Serogroup/ Menactra Lot #	Baseline GMT	Estimate of Baseline GMT	Estimate of Max GMT Effect Post-vaccination	Difference of Treatment Effect (Max-Min)	Anti-Log_2 of The Difference In Treatment Effect (Max-Min)	2-sided 90% CI for the Anti-Log_2 of the Difference in Treatment Effect
Serogroup A						
Lot 1	240.0	-0.897	0.304	0.304	1.234	(1.090, 1.397)
Lot 2	271.5		0.287			
Lot 3	247.6					
Serogroup C						
Lot 1	73.7	-0.809	0.283	0.446	1.362	(1.143, 1.624)
Lot 2	57.9		0.446			
Lot 3	79.8					
Serogroup Y						
Lot 1	242.7	-0.751	-0.460	0.587	1.502	(1.293, 1.745)
Lot 2	185.6		-0.587			
Lot 3	205.6					
Serogroup W135						
Lot 1	47.4	-0.734	-0.301	0.326	1.253	(1.059, 1.483)
Lot 2	48.3		0.025			
Lot 3	44.5					

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

Proportions with four-fold or greater increases in SBA-BR titer:
The minimum proportion of participants achieving a four-fold or greater increase in SBA-BR antibody to serogroup C was 83.2% [415/499, lot 3], 71.6% [348/486, lot 2] for serogroup Y, 86.1% [426/495, lot 1] for serogroup W135, and 81.6% [407/499, lot 3] for serogroup A (MTA-14 Table 5). The maximum proportion of participants achieving a four-fold or greater increase in SBA-BR antibody to serogroup C was 89.5% [lot 2], 80.6% [lot 3] for serogroup Y, 91.8% [lot 3] for serogroup W135, and 85.4% [lot 2] for serogroup A.

MTA-14 Table 5: Percentage of Participants Achieving a ≥ Four-fold Increase in SBA-BR Antibody Titer, with 95%CI

Serogroup	Menactra Lot 1 N=495		Menactra Lot 2 N=486		Menactra Lot 3 N=499	
	$p_{Menactra}$†	95% CI	$p_{Menactra}$†	95% CI	$p_{Menactra}$†	95% CI
A	85.1%	81.60, 88.08	85.4%	81.93, 88.41	81.6%	77.88, 84.87
C	85.9%	82.47, 88.81	89.5%	86.43, 92.09	83.2%	79.59, 86.34
Y	74.9%	70.89, 78.71	71.6%	67.37, 75.57	80.6%	76.81, 83.94
W-135	86.1%	82.69, 88.99	88.1%	84.85, 90.81	91.8%	89.02, 94.04

*n: number of participants with ≥ 4-fold rise SBA-BR titer from baseline. N: total number of participants with valid serology data.
† $p_{Menactra}$: percentage of Menactra participants with a ≥ 4-fold rise in SBA-BR titer post-vaccination compared with baseline.

Secondary hypothesis testing:
Immune responses to the three Menactra lots were considered to be consistent if the upper limit of the one-sided 95% confidence interval for the difference in two proportions was less than 10%. For each serogroup, the proportions compared were the maximum and minimum percent of participants achieving a four-fold or greater increase in SBA-BR post-vaccination, compared to baseline. This hypothesis was achieved for serogroup A (8.5%) and W135 (9.6%), but not for serogroups C (10.6%) and Y (14.3%) (MTA-14 Table 6).

MTA-14 Table 6: Secondary Hypothesis Testing #2
Number and Percentage of Participants with a ≥ Four-fold Increase in SBA-BR Titer

Serogroup	Menactra Lot 1 N=495		Menactra Lot 2 N=486		Menactra Lot 3 N=499		Difference $p_{(Max)} - p_{(Min)}$	Upper Limit of the 2-sided 95% CI of the Difference§
	n*	$p_{Menactra}$†	n*	$p_{Menactra}$†	n*	$p_{Menactra}$†		
A	421	85.1%	415	85.4%	407	81.6%	3.8%	8.5
C	425	85.9%	435	89.5%	415	83.2%	6.3%	10.6
Y	371	74.9%	348	71.6%	402	80.6%	9.0%	14.3
W-135	426	86.1%	428	88.1%	458	91.8%	5.7%	9.6

*n: number of participants with ≥ 4-fold rise from baseline SBA-BR titer. N: total number of participants with valid serology data.
† $p_{Menactra}$: 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 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 participants with serogroup A SBA-BR antibody less than 1:8 pre-vaccination, in both groups, achieved seroconversion. The minimum proportion of Menactra participants who achieved 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].

7.1.5.9.3 Safety

Overall safety profile:
A summary of participants with each type of adverse event, for the Menactra lot consistency and the Menomune safety comparisons, is presented in MTA-14 Table 7 and 8:

MTA-14: Menactra Lot Consistency, Overall Participant Safety Profile

Type of AE	Menactra Lot 1		Menactra Lot 2		Menactra Lot 3	
	n/N*	%†	n/N*	%†	n/N*	%†
Immediate reactions (within 30 minutes)	0/527	0.0	0/528	0.0	2/527	0.4
Solicited local reactions (Days 0-7)	285/521	54.7	278/521	53.4	296/522	56.7
95% Confidence Interval		50.32, 59.04		48.97, 57.71		52.33, 61.00
Solicited systemic reactions (Days 0-7)	311/521	59.7	310/521	59.5	320/522	61.3
95% Confidence Interval		55.34, 63.94		55.15, 63.75		56.97, 65.50
Unsolicited adverse events (Days 0-28)	141/517	27.3	118/509	23.2	126/519	24.3
Unsolicited significant adverse events (Day 29- Month 6)	32/493	6.5	21/480	4.4	18/492	3.7
All serious adverse events (Day 0-Month 6)	12/527	2.3	5/528	0.9	5/527	0.9

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

MTA-14 Table 8: Menomune® Comparison Overall Participant Safety Profile, 26-55 years old

Type of AE	Menactra		Menomune®	
	n/N*	%†	n/N*	%†
Immediate reactions (within 30 minutes)	0/686	0	0/458	0
Solicited local reactions (Days 0-7)	290/685	42.3	118/454	26
95% Confidence Interval		38.60, 46.14		22.01, 30.28
Solicited systemic reactions (Days 0-7)	366/685	53.4	224/455	49.2
95% Confidence Interval		49.61, 57.22		44.55, 53.93
Unsolicited adverse events (Days 0-28)	169/679	24.9	101/445	22.7
Unsolicited significant adverse events (Day 29- Month 6)	46/653	7.0	31/427	7.3
All serious adverse events (Day 0-Month 6)	11/686	1.6	12/458	2.6

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

Immediate reactions: Four reactions were reported by two Menactra participants (lot #3), and no Menomune® participants. One participant experienced lightheadness, and the other participant developed

syncope; both symptoms resolved on the same day. The latter participant also reported vertigo and nausea, which resolved after two and five days, respectively.

Local reactions:

Menactra lot consistency comparison (18-55 years old):
The occurrence of any injection site reaction reported by Menactra lot 1, 2 and 3 recipients was similar. Injection site pain was most frequent, and overall, reported by 50.7%, 48.8% and 52.7% of Menactra lot 1, 2 and 3 participants, respectively; 8.1%, 9.4% and 7.3% of participants experienced moderate pain. The severe local adverse event rate was 1.0%, 0.8% and 1.3% in the Menactra lot 1, 2 and 3 vaccine groups respectively.

MTA-14 Table 9: Menactra Lot 1-3 (18-55 years old)
Local adverse reactions (Days 0-7)

		Menactra Lot 1 N= 521			Menactra Lot 2 N= 521			Menactra Lot 3 N= 522		
Reaction	**Severity**	**n***	**%†**	**95% CI**	**n***	**%†**	**95% CI**	**n***	**%†**	**95% CI**
Redness										
	Any	60	11.5	8.90, 14.57	75	14.4	11.49, 17.71	63	12.1	9.40, 15.18
< 1 inch	**Mild**	50	9.6	7.21, 12.46	64	12.3	9.59, 15.41	54	10.3	7.87, 13.28
1 – 2 inches	**Moderate**	6	1.2	0.42, 2.49	9	1.7	0.79, 3.25	6	1.1	0.42, 2.48
> 2 inches	**Severe**	4	0.8	0.21, 1.95	2	0.4	0.05, 1.38	3	0.6	0.12, 1.67
Swelling										
	Any	58	11.1	8.56, 14.15	55	10.6	8.05, 13.52	56	10.7	8.21, 13.70
< 1 inch	**Mild**	47	9.0	6.70, 11.82	46	8.8	6.54, 11.60	50	9.6	7.19, 12.43
1 – 2 inches	**Moderate**	9	1.7	0.79, 3.25	7	1.3	0.54, 2.75	2	0.4	0.05, 1.38
> 2 inches	**Severe**	2	0.4	0.05, 1.38	2	0.4	0.05, 1.38	4	0.8	0.21, 1.95
Induration										
	Any	75	14.4	11.49, 17.71	90	17.3	14.13, 20.80	92	17.6	14.45, 21.17
< 1 inch	**Mild**	62	11.9	9.25, 14.99	73	14.0	11.15, 17.29	79	15.1	12.17, 18.50
1 – 2 inches	**Moderate**	11	2.1	1.06, 3.75	16	3.1	1.77, 4.94	9	1.7	0.79, 3.25
> 2 inches	**Severe**	2	0.4	0.05, 1.38	1	0.2	0.00, 1.06	4	0.8	0.21, 1.95
Pain										
	Any	264	50.7	46.29, 55.05	254	48.8	44.38, 53.14	275	52.7	48.30, 57.04
	Mild	222	42.6	38.32, 46.98	204	39.2	34.94, 43.49	236	45.2	40.88, 49.59
	Moderate	42	8.1	5.87, 10.74	49	9.4	7.04, 12.24	38	7.3	5.20, 9.86
	Severe	0	0.0	0.00, 0.57	1	0.2	0.00, 1.06	1	0.2	0.00, 1.06

*n: number of participants reporting at least one event in this category. Local adverse event information was not provided by 23 participants (Menactra lot 1 n= 7, lot 2= 7, lot 3= 5). 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) symptom present, but arm movement not affected, 2= (moderate) limits usual arm movement, 3= (severe) disabling

Menomune safety comparison (26-55 years old):
The safety data from all Menactra participants 26-55 years old (lots #1-3) were combined and compared to data from age-matched Menomune® recipients (MTA-14 Table 10). The occurrence of any injection site reaction was reported by 43.3% [290/685] and 26.0% [118/454] of Menactra and Menomune® recipients, respectively. Mild pain was 1.8 times more frequent (38.6% vs. 19.6%) in Menactra than Menomune® participants in the first 3 days following vaccination, and present 3.4 times (4.4 vs. 1.3%) more commonly during Days 4-7. Moderate pain, during in first 3 days after vaccination, was also more common in the Menactra than the Menomune® group (4.4 vs. 0.9%). The frequencies of mild swelling and induration, in the first 3 days post-vaccination, occurred approximately 2 times more often in Menactra than Menomune®

participants. Eleven severe local reactions occurred in six Menactra participants and no Menomune® participants. Four individuals experienced two or more severe adverse events, which included severe swelling, induration and/or erythema.

MTA-14 Table 10: Menomune® Safety Comparison (26-55 years old)
Local adverse reactions (Days 0-3, 4-7)

Reaction	Severity	Timepoint	Menactra N= 684 (Days 0-3); N= 685 (Days 4-7) n*	%†	95% CI	[illegible] n*	%	[illegible]
Redness								
	Any	Days 0-3	71	10.4	8.20, 12.91	44	9.7	7.13, 12.79
		Days 4-7	17	2.5	1.45, 3.94	7	1.5	0.62, 3.15
< 1 inch	**Mild**	Days 0-3	57	8.3	6.37, 10.66	40	8.8	6.37, 11.80
		Days 4-7	11	1.6	0.80, 2.86	6	1.3	0.49, 2.85
1 – 2 inches	**Moderate**	Days 0-3	11	1.6	0.81, 2.86	4	0.9	0.24, 2.24
		Days 4-7	4	0.6	0.16, 1.49	1	0.2	0.01, 1.22
> 2 inches	**Severe**	Days 0-3	3	0.4	0.09, 1.28	0	0.0	0.00, 0.66
		Days 4-7	2	0.3	0.04, 1.05	0	0.0	0.00, 0.66
Swelling								
	Any	Days 0-3	73	10.7	8.46, 13.23	19	4.2	2.54, 6.46
		Days 4-7	20	2.9	1.79, 4.47	3	0.7	0.14, 1.92
< 1 inch	**Mild**	Days 0-3	61	8.9	6.89, 11.31	18	4.0	2.37, 6.19
		Days 4-7	15	2.2	1.23, 3.59	2	0.4	0.05, 1.58
1 – 2 inches	**Moderate**	Days 0-3	10	1.5	0.70, 2.67	1	0.2	0.01, 1.22
		Days 4-7	4	0.6	0.16, 1.49	1	0.2	0.01, 1.22
> 2 inches	**Severe**	Days 0-3	2	0.3	0.04, 1.05	0	0.0	0.00, 0.66
		Days 4-7	1	0.1	0.00, 0.81	0	0.0	0.00, 0.66
Induration								
	Any	Days 0-3	90	13.2	10.71, 15.92	24	5.3	3.42, 7.76
		Days 4-7	25	3.6	2.38, 5.34	4	0.9	0.24, 2.24
< 1 inch	**Mild**	Days 0-3	76	11.1	8.85, 13.71	22	4.8	3.06, 7.24
		Days 4-7	19	2.8	1.68, 4.30	4	0.9	0.24, 2.24
1 – 2 inches	**Moderate**	Days 0-3	11	1.6	0.81, 2.86	2	0.4	0.05, 1.58
		Days 4-7	5	0.7	0.24, 1.70	0	0.0	0.00, 0.66
> 2 inches	**Severe**	Days 0-3	3	0.4	0.09, 1.28	0	0.0	0.00, 0.66
		Days 4-7	1	0.1	0.00, 0.81	0	0.0	0.00, 0.66
Pain								
	Any	Days 0-3	264	38.6	34.93, 42.36	89	19.6	16.05, 23.56
		Days 4-7	3	4.5	3.10, 6.36	7	1.5	0.62, 3.15
	Mild	Days 0-3	233	34.1	30.52, 37.75	85	18.7	15.24, 22.62
		Days 4-7	30	4.4	2.97, 6.19	6	1.3	0.49, 2.85
	Moderate	Days 0-3	31	4.5	3.10, 6.37	4	0.9	0.24 2.24
		Days 4-7	1	0.1	0.00, 0.81	1	0.2	0.01, 1.22
	Severe	Days 0-3	0	0.0	0.00, 0.44	0	0.0	0.00, 0.66
		Days 4-7	0	0.0	0.00, 0.44	0	0.0	0.00, 0.66

*n: number of participants reporting at least one event in this category. Local adverse event information during Days 0-3 was not provided by 6 participants (Menactra n= 2, Menomune® n= 4). Local adverse event information during Days 4-7 was not provided by 5 participants (Menactra n= 1, Menomune® n= 4). 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) symptom present, but arm movement not affected, 2= (moderate) limits usual arm movement, 3= (severe) disabling

Systemic reactions:

Menactra lot consistency comparison (18-55 years old):

Headache was most frequent systemic reaction, and occurred in 42.0%, 38.0% and 40.0% of Menactra lot 1, 2 and 3 recipients, respectively. Mild headache occurred in 29.6% [lot 1], 27.6% [lot 2] and 29.3% [lot 3] of participants, and started mainly within the first 3 days following vaccination. Mild headache, present during Days 4-7, was reported by 16.3%, 14.8% and 12.8% of Menactra participants, respectively. Fatigue occurred in 32.2% [lot 1], 33.0% [lot 2], and 35.1% [lot 3] of Menactra participants. Mild fatigue, present during Days 4-7, was reported by 10.4%, 10.9% and 10.3% of Menactra participants, respectively. One Menactra participant [lot 3] reported T104.0F, which started one day after vaccination, and resolved the same day.

Excluding rashes, 49 severe systemic reactions occurred in 44 Menactra participants. The severe systemic reaction rate was 1.9%, 1.9% and 1.3%, respectively. Five Menactra participants in each of the lot 1 and 2 groups, and 2 Menactra participants in the lot 3 group, reported ≥2 severe systemic reactions. Of the Menactra participants with multiple reactions, all experienced severe fatigue or malaise. Two Menactra participants [lot 1, lot2] experienced more than 3 severe systemic reactions. Both reported arthralgia, anorexia, fatigue and malaise; in addition, the Menactra lot 1 recipient reported severe chills, vomiting and diarrhea, and the Menactra lot 2 participant reported severe headache.

Rash, occurring within 7 days after vaccination, was reported by 22 participants [lot 1 n=8, lot 2 n=7, lot 3 n=7]. Descriptions of localized rash did not differ from results reported from other trials. One Menactra participant [lot 2] reported a hive-like generalized rash two days after vaccination. The rash was described as red, raised, itchy and non-blanching. The rash responded to cetirizine (Zyrtec), and resolved after 1.5 days.

MTA-14 Table 11: Menactra Lot 1-3 (18-55 years old)
Systemic adverse reactions (Days 0-7)

		Menactra Lot 1			Menactra Lot 2			Menactra Lot 3		
Reaction	**Severity**	**n/N***	**%†**	**95% CI‡**	**n/N***	**%†**	**95% CI**	**n/N***	**%†**	**95% CI**
Fever										
	Any	4/515	0.8	0.21, 1.98	7/516	1.4	0.55, 2.78	3/516	0.6	0.12, 1.69
38.0°C-38.9°C	**Mild**	4/515	0.8	0.21, 1.98	6/516	1.2	0.43, 2.51	2/516	0.4	0.05, 1.39
39.0°C-39.9°C	**Moderate**	0/515	0.0	0.00, 0.58	1/516	0.2	0.00, 1.08	0/516	0.0	0.00, 0.58
≥ 40.0°C	**Severe**	0/515	0.0	0.00, 0.58	0/516	0.0	0.00, 0.58	1/516	0.2	0.00, 1.08
Headache										
	Any	219/521	42.0	37.76, 46.40	198/521	38.0	33.82, 42.33	209/522	40.0	35.81, 44.38
	Mild	154/521	29.6	25.67, 33.68	144/521	27.6	23.84, 31.69	153/522	29.3	25.44, 33.42
	Moderate	62/521	11.9	9.25, 14.99	51/521	9.8	7.38, 12.67	54/522	10.3	7.87, 13.28
	Severe	3/521	0.6	0.12, 1.67	3/521	0.6	0.12, 1.67	2/522	0.4	0.05, 1.38
Fatigue										
	Any	168/521	32.2	28.25, 36.45	172/521	33.0	28.99, 37.24	183/522	35.1	30.96, 39.32
	Mild	126/521	24.2	20.57, 28.10	123/521	23.6	20.02, 27.49	136/522	26.1	22.34, 30.04
	Moderate	38/521	7.3	5.21, 9.87	46/521	8.8	6.54, 11.60	44/522	8.4	6.19, 11.15
	Severe	4/521	0.8	0.21, 1.95	3/521	0.6	0.12, 1.67	3/522	0.6	0.12, 1.67
Malaise										
	Any	116/521	22.3	18.76, 26.09	110/521	21.1	17.69, 24.87	123/522	23.6	19.99, 27.44
	Mild	83/521	15.9	12.89, 19.36	85/521	16.3	13.24, 19.77	87/522	16.7	13.57, 20.15
	Moderate	28/521	5.4	3.60, 7.67	22/521	4.2	2.66, 6.32	36/522	6.9	4.88, 9.42
	Severe	5/521	1.0	0.31, 2.23	3/521	0.6	0.12, 1.67	0/522	0.0	0.00, 0.57

Cont. MTA-14 Table 11: Menactra Lot 1-3 (18-55 years old)
Systemic adverse reactions (Days 0-7)

Reaction	Severity	Menactra Lot 1 n/N*	%	95% CI	Menactra Lot 2 n/N*	%	95% CI	Menactra Lot 3 n/N*	%	95% CI
Chills										
	Any	36/521	6.9	4.89, 9.44	30/521	5.8	3.92, 8.12	48/522	9.2	6.86, 12.01
	Mild	28/521	5.4	3.60, 7.67	25/521	4.8	3.13, 7.00	38/522	7.3	5.20, 9.86
	Moderate	7/521	1.3	0.54, 2.75	4/521	0.8	0.21, 1.95	10/522	1.9	0.92, 3.49
	Severe	1/521	0.2	0.00, 1.06	1/521	0.2	0.00, 1.06	0/522	0.0	0.00, 0.57
Arthralgia										
	Any	103/521	19.8	16.43, 23.45	93/521	17.9	14.66, 21.41	103/522	19.7	16.40, 23.41
	Mild	75/521	14.4	11.49, 17.71	75/521	14.4	11.49, 17.71	83/522	15.9	12.87, 19.32
	Moderate	25/521	4.8	3.13, 7.00	14/521	2.7	1.48, 4.47	20/522	3.8	2.36, 5.86
	Severe	3/521	0.6	0.12, 1.67	4/521	0.8	0.21, 1.95	0/522	0.0	0.00, 0.57
Anorexia										
	Any	53/521	10.2	7.71, 13.09	61/521	11.7	9.08, 14.78	65/522	12.5	9.74, 15.59
Skips 1 meal	**Mild**	39/521	7.5	5.38, 10.09	50/521	9.6	7.21, 12.46	53/522	10.2	7.70, 13.07
Skips 2 meals	**Moderate**	13/521	2.5	1.34, 4.23	8/521	1.5	0.67, 3.00	12/522	2.3	1.19, 3.98
Skips ≥ 3 meals	**Severe**	1/521	0.2	0.00, 1.06	3/521	0.6	0.12, 1.67	0/522	0.0	0.00, 0.57
Diarrhea										
	Any	91/521	17.5	14.30, 21.00	81/521	15.5	12.54, 18.95	95/522	18.2	14.98, 21.78
1-2 episodes	**Mild**	68/521	13.1	10.28, 16.25	63/521	12.1	9.42, 15.20	77/522	14.8	11.82, 18.09
3-4 episodes	**Moderate**	20/521	3.8	2.36, 5.87	16/521	3.1	1.77, 4.94	15/522	2.9	1.62, 4.70
> 5 episodes	**Severe**	3/521	0.6	0.12, 1.67	2/521	0.4	0.05, 1.38	3/522	0.6	0.12, 1.67
Seizures (Y/N)										
Yes	**Days 0-7**	0/521	0.0	0.00, 0.57	0/521	0.0	0.00, 0.57	7/522	1.3	0.54, 2.74
Rash										
Any rash	**Days 0-7**	8/521	1.5	0.67, 3.00	7/521	1.3	0.54, 2.75	0/522	0.0	0.00, 0.57

*n: number of participants reporting at least one event in this category. Information for each systemic adverse event was not provided by 23 participants (Menactra lot 1 n= 7, lot 2= 7, lot 3= 5). Also, for 37 additional participants, safety information was available, but temperature was not recorded. Percentages are based on the total number of participants who did submit safety information at each time point.

†%: n/N expressed as a percentage.

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

Menomune safety comparison (26-55 years old):

The safety data from all Menactra participants 26-55 years old (lots #1-3) were combined and compared to data from age-matched Menomune® recipients. In both groups, headache was most frequent, and occurred in 35.0% [240/685] of Menactra participants and 33.6% [153/455] Menomune® participants. Mild headache was reported by 21.8% of Menactra participants and 20.2% of Menomune® participants, respectively, and started mainly within the first three days following vaccination. During Days 4-7, 13.1% of Menactra participants and 13.2% of Menomune® participants reported headache. Similar trends were observed for the rate of fatigue. Mild arthralgia, during the first 3 days after vaccination, occurred in 11.4% of Menactra participants and 8.1% of Menomune® participants, while 2.8% and 2.0%, respectively, reported moderate arthralgia. Frequencies of mild and moderate arthralgia present on Days 4-7 were ~50% lower than corresponding frequencies reported in the first 3 days post-vaccination. Chills, overall, were reported by 6.6% of Menactra participants and 3.3% of Menomune® participants. Rash, occurring within 7 days after vaccination, was reported by 17 participants [Menactra n=7, Menomune® n=11]. All rashes were localized, and descriptions of the rash were consistent with results reported from other trials.

Excluding rashes, 12 severe systemic reactions occurred in 8 Menactra participants, and 27 severe reactions in 14 Menomune® participants. Four of eight Menactra participants and seven of 13 Menomune® participants reported two or more severe systemic reactions.

MTA-14 Table 12: Menomune® Comparison (26-55 years old)
Systemic adverse reactions (Days 0-7)

Reaction	Severity	Menactra n/N*	Menactra %†	Menactra 95% CI	Menomune® n/N*	Menomune® %†	Menomune® 95% CI
Fever							
	Any	4/683	0.6	0.16, 1.49	2/453	0.4	0.05, 1.59
38.0°C-38.9°C	**Mild**	4/683	0.6	0.16, 1.49	2/453	0.4	0.05, 1.59
39.0°C-39.9°C	**Moderate**	0/683	0.0	0.00, 0.44	0/453	0.0	0.00, 0.66
≥ 40.0°C	**Severe**	0/683	0.0	0.00, 0.44	0/453	0.0	0.00, 0.66
Headache							
	Any	240/685	35.0	31.46, 38.74	153/455	33.6	29.29, 38.17
	Mild	174/685	25.4	22.18, 28.84	113/455	24.8	20.93, 29.07
	Moderate	63/685	9.2	7.14, 11.61	35/455	7.7	5.42, 10.54
	Severe	3/685	0.4	0.09, 1.27	5/455	1.1	0.36, 2.55
Fatigue							
	Any	192/685	28.0	24.69, 31.56	114/455	25.1	21.14, 29.30
	Mild	139/685	20.3	17.34, 23.50	88/455	19.3	15.81, 23.27
	Moderate	49/685	7.2	5.34, 9.35	20/455	4.4	2.71, 6.71
	Severe	4/685	0.6	0.16, 1.49	6/455	1.3	0.49, 2.85
Malaise							
	Any	134/685	19.6	16.65, 22.73	80/455	17.6	14.20, 21.40
	Mild	99/685	14.5	11.90, 17.31	56/455	12.3	9.43, 15.68
	Moderate	33/685	4.8	3.34, 6.70	16/455	3.5	2.02, 5.65
	Severe	2/685	0.3	0.04, 1.05	8/455	1.8	0.76, 3.43
Chills							
	Any	45/685	6.6	4.83, 8.69	15/454	3.3	1.86, 5.39
	Mild	39/685	5.7	4.08, 7.70	11/454	2.4	1.22, 4.29
	Moderate	6/685	0.9	0.32, 1.90	2/454	0.4	0.05, 1.58
	Severe	0/685	0.0	0.00, 0.44	2/454	0.4	0.05, 1.58
Arthralgia							
	Any	104/685	15.2	12.58, 18.09	57/455	12.5	9.63, 15.92
	Mild	81/685	11.8	9.50, 14.48	41/455	9.0	6.54, 12.03
	Moderate	23/685	3.4	2.14, 5.00	14/455	3.1	1.69, 5.11
	Severe	0/685	0.0	0.00, 0.44	2/455	0.4	0.05, 1.58
Anorexia							
	Any	64/685	9.3	7.27, 11.77	35/454	7.7	5.43, 10.56
Skips 1 meal	**Mild**	51/685	7.4	5.59, 9.67	27/454	5.9	3.96, 8.54
Skips 2 meals	**Moderate**	12/685	1.8	0.91, 3.04	7/454	1.5	0.62, 3.15
Skips ≥ 3 meals	**Severe**	1/685	0.1	0.00, 0.81	1/454	0.2	0.01, 1.22
Vomiting							
	Any	8/685	1.2	0.51, 2.29	6/455	1.3	0.49, 2.85
1 episode	**Mild**	6/685	0.9	0.32, 1.90	3/455	0.7	0.14, 1.91
2 episodes	**Moderate**	2/685	0.3	0.04, 1.05	3/455	0.7	0.14, 1.91
>3 episodes	**Severe**	0/685	0.0	0.00, 0.44	0/455	0.0	0.00, 0.66

Cont. MTA-14 Table 12: Menomune® Comparison (26-55 years old) Systemic adverse reactions (Days 0-7)							
		Menactra			Menomune®		
Reaction	Severity	n/N*	%†	95% CI	n/N*	%†	95% CI
Diarrhea							
	Any	105/685	15.3	12.71, 18.25	70/455	15.4	12.19, 19.03
1-2 episodes	**Mild**	82/685	12.0	9.63, 14.64	51/455	11.2	8.46, 14.47
3-4 episodes	**Moderate**	21/685	3.1	1.91, 4.65	16/455	3.5	2.02, 5.65
> 5 episodes	**Severe**	2/685	0.3	0.04, 1.05	3/455	0.7	0.14, 1.91
Seizures (Y/N)							
Yes	**Days 0-7**	0/685	0.0	0.00, 0.44	0/454	0.0	0.00, 0.66
Rash							
Any rash	**Days 0-7**	7/685	1.0	0.41, 2.09	11/454	2.4	1.22, 4.29

*n: number of participants reporting at least one event in this category. Systemic adverse event information was not provided by 5 participants (Menactra n= 2, Menomune® n= 3). Percentages are based on the total number of participants who did submit safety information at each time point.
†%: n/N expressed as a percentage.
Headache, chills, arthralgia, fatigue, malaise: 0= none, 1= aware, easily tolerated, 2= interferes with usual activities, 3= disabling

Secondary Hypothesis #1:
The upper limit of the 2-sided 95% CI for the difference in maximum and minimum proportions, for Menactra lots 1, 2, and 3, was less than 10%.

MTA-14 Table 13: Secondary Hypothesis Testing #1 Menactra Lot Consistency Comparison (18-55 years old) Percentage of Participants With At Least One Severe Solicited Systemic Reaction (Days 0-7)				
Menactra Lot 1	Menactra Lot 2	Menactra Lot 3	Difference $p_{(Max)} - p_{(Min)}$	Upper Limit of the 2-sided 95% CI§ of the Ratio
N= 521	N= 521	N= 522		
$p_{Menactra1}$	$p_{Menactra2}$	$p_{Menactra3}$		
0.035	0.033	0.027	0.008	0.03

N= Total number of participants for whom safety information is available.
†$p_{Menactra}$: proportion of participants with at least one severe systemic reaction or rash in Menactra lot 1,2 and 3 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.

Secondary Hypothesis #3:
The upper limit of the 2-sided 95% CI for the difference in maximum and minimum proportions, for Menactra and Menomune® participants 26-55 years old, was less than 10% (MTA-14 Table 14).

MTA-14 Table 14: Secondary Hypothesis Testing #3, Menomune Safety Comparison (26-55 years old) Percentage of Participants With At Least One Severe Solicited Systemic Reaction			
Menactra	Menomune®	Difference $p_{Menactra} - p_{Menomune®}$	Upper Limit of the 2-sided 95% CI§ of the Ratio
N= 685	N= 455		
$p_{Menactra1}$	$p_{Menomune}$		
0.022	0.055	-0.033	-0.01

*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.

Serious adverse events:
Two deaths occurred during the study. 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.

7.1.5.10 Reviewer summary and conclusions for study MTA-14

Safety:
Menactra lot consistency comparison (18-55 years old):
The safety profile was similar among the three Menactra vaccine groups, and to corresponding events reported for MTA-09 Menactra study participants.

Menomune® safety comparison (26-55 years old):
Except for the frequency of overall pain in the Menomune group, which was 19.6%, the results obtained were similar to the results for MTA-09 Menactra and Menomune® study participants. The conclusions for this study population are the same as for MTA-09.

Immunogenicity:
Each of the three Menactra lots was immunogenic, although the elicited bactericidal antibody responses to serogroup C and Y were mildly variable. The primary hypothesis for lot consistency was to demonstrate that for each Menactra vaccine lot, the upper limit of the 2-sided 90% CI of the difference in treatment effect (max-min) was less than 1.5, for each serogroup. This criterion was achieved for serogroup A and W135, but not for serogroups C or Y. The treatment effect difference for serogroups C and Y was not widely variable, and was less than $\log_2$ (2.0). Similar results were obtained when the primary immunogenicity analysis was based on the intent-to-treat population, and when immune responses to the three Menactra vaccine lots were assessed by the proportion of participants who achieved at least a four-fold SBA-BR antibody increase post-vaccination, for each serogroup. As a secondary endpoint, the three Menactra vaccine lots were considered equivalent if the upper limit of the 2-sided 95% CI fore the difference in two proportions was less than 10%. For each serogroup, the maximum and minimum percentage of participants with a $\geq$ four-fold SBA-BR antibody increase were compared. The conclusions from the analysis of this secondary immunogenicity endpoint were the same as for the primary immunogenicity endpoint. For serogroup A and W135, the calculated upper limit was 8.5% and 9.6%, respectively, whereas the corresponding results for serogroups C and Y were 10.6% and 14.3%. Possible explanations for these results could be variable vaccine-induced antibody response in the studied population, SBA-BR assay variability, inconsistent manufactured vaccine lot(s), or relatively stringent statistical criteria for the proposed endpoint.

8.0 Supporting Clinical Studies:

8.1 Study #603-01/00: Phase 1 Dose Escalation, Safety and Immunogenicity Study With Meningococcal A,C,Y,W135-diphtheria Conjugate Vaccine In Healthy Adults, Toddlers and Infants.

Study Design: This study was an open-label, dose-escalation, single center trial in the United States. Enrollment proceeded in a step-wise approach, initially in 90 adults (18-55 years old), then 30 toddlers (12-22 months old) and lastly, 90 infants (6-12 weeks old). Participants were vaccinated, intramuscularly, with 1 μg, 4 μg, or 10 μg/PS dosage level of the meningococcal polysaccharide diphtheria conjugate vaccine. Adults received a single vaccination (n=30/gr), toddlers received two vaccinations one month apart (n=10/gr), and infants received three vaccinations two months apart (n=30/gr). Enrolled infants then received a booster dose, 15-19 months old, with Menomune® vaccine. Sera were collected at scheduled visits for all participants (Days 0 and 28-30 for adults; Days 0, 60 and 90 for toddlers; and at 6 and 7 months for infants), and tested for immunogenicity to meningococcal antigens by SBA-BR and ELISA for IgG. Complete information for the booster stage was not included in the application but is anticipated to be included as a supplement to in the final clinical study report. Only the sections of this study, which relate to the meningococcal safety and immunogenicity evaluation in adults, and the safety evaluation in toddlers and infants (primary series), are covered in this review.

Study period: Adults: 7/07/97 to 10/02/97. Toddler: 09/18/97 to 03/12/98.
Infant: 03/24/98 to 05/11/99; booster: 05/26/99 to 03/09/00.

Results:

Safety: Adult tolerated local reactions. Chills along with systemic symptoms (e.g. headache, malaise, arthralgia, anorexia) in occurred in four adults (1 μg n= 1; 4 μg n=1; or 10 μg n=2). One adult reported severe chills (4 μg,). No serious adverse events were reported in adults. High fever (T39-39.9 C) occurred in three toddlers; concurrent URI symptoms were noted in one toddler. The significance of high fever is difficult to interpret due to the small number of toddlers enrolled in this study. One death occurred in a 5 month old infant due to SIDS, ~1 month after the 2nd vaccination (10ug), which was determined to be unrelated to vaccination by the investigator.

Immunogenicity: Of 30 planned participants, 28 adults given a single dose (4ug) of Menactra had evaluable results.

SBA-BR: Of 28 adults, 71%, 89%, 82%, and 86% of the vaccine recipients achieved a 4-fold bactericidal antibody rise post-vaccination to serogroups A, C, Y, and W135, respectively. For serogroup C, 89% of recipients achieved post-vaccination titer ≥1:128, compared with 36% with the same titer at baseline. In addition, 85% of vaccinees achieved a post-vaccination titer ≥1:8 to serogroup Y, compared with 46% with the same titer at baseline. For serogroup W-135, 86% of recipients achieved a post-vaccination titer ≥1:8, compared with 46% with the same titer at baseline.

ELISA: A post-vaccination GMC ≥ 2ug/ml to serogroups A, C, Y, and W135, respectively, were achieved in 96%, 75%, 61% and 68% of 4ug recipients.

Summary: A single dose in adults was immunogenic, and participants achieved adequate bactericidal responses to all serogroups; however, antibody responses were slightly lower compared with historic meningococcal polysaccharide [Menomune® A,C,Y,W135] controls. All serum samples were analyzed with an SBA using baby rabbit compliment. The choice of selected dose and dosing regimen for Phase II and III studies in persons 11-55 years old was supported by the safety and immunogenicity results.

8.2 Study 603-02/00: 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 Children in the U.S.

Design: This study was a randomized, modified double-blind (different routes of administration), active-controlled, multi-center trial conducted in the United States. A total of 1398 (Menactra n=696, Menomune® n= 702) healthy children 2 -10 years old were enrolled. Eligible participants received a single dose of either Menactra or Menomune®. Since the routes of administration differed, study personnel administering the vaccine were different from personnel collecting the safety data. Routine childhood vaccines were not administered with the study or control vaccine. Both safety and immunogenicity of Menactra were evaluated in this study. Only study elements related to the safety are described hereafter.

Study period: April 26, 2000 to December 5, 2001.

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

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

Safety results:
The occurrence of local reactions, during the 7 day post-vaccination period, were reported in 58.8% [407/692] and 58.3% [408/700] of Menactra and Menomune® participants, respectively. The frequency of solicited systemic reactions, overall, occurred in 53.5% [371/693] and 52.0% [364/700] of Menactra and Menomune® participants, respectively. Twenty-three participants (Menactra n= 16 Menomune n= 7) reported a serious adverse event. The events reported were primarily hospitalizations for an acute condition, e.g. gastroenteritis with dehydration, pneumonia, reactive airways disease exacerbation. Bacteremia occurred in two Menomune® participants, and *S. pneumoniae* was isolated from the blood culture in both cases. Possible bacteremia was reported for a Menactra participant. This study participant was a 3 year old child who developed fever and vomiting 16 days following vaccination. The white blood count was 18,500, but no organism was isolated from the blood culture. The participant responded to antibiotic treatment and recovered completely. Two Menactra participants developed a febrile seizure, and both had an uneventful recovery. The SAEs reported were not unusual for the study population

8.3 Study MTA-08: A Comparative Trial of the Safety 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 Children Aged 2 to 10 Years in the US and Chile.

Design: This study was a randomized, modified double-blind (different routes of administration), active-controlled, multi-center trial conducted in the U.S. and Chile. A total of 3232 (Menactra n= 1712, Menomune® n=1519; n=2000 US, 1232 Chile) healthy children 2 -10 years old were enrolled. Only children who had received at least 4 doses of a DTP-containing vaccine more than 28 days prior to enrollment were eligible for participation in this study. Participants received a single dose of either Menactra or Menomune® vaccine. The vaccine received by 1 participant (subject #3517) could not be verified at the time of this report. Routine childhood vaccines were not administered with the study or control vaccine.

Study period: June 17, 2002 to July 1, 2003.

Surveillance:
Monitored parameters: Except for rash, arthralgia, and seizures, which were included in the queries for solicited systemic adverse events in this study, the monitored safety parameters for local, systemic, unsolicited, significant and serious adverse events, and the surveillance for all events, was the same as described for study 603-02/00.

Safety results:
The occurrence of local reactions, during the 7 day post-vaccination period, were reported in 47.0% [801/1704] and 35.7% [541/1515] of Menactra and Menomune® participants, respectively. The frequency of solicited systemic reactions, overall, occurred in 33.8% [577/1705] and 33.9% [514/1515] of Menactra and Menomune® participants, respectively. Twenty-three participants (Menactra n= 11 Menomune n= 11, undetermined vaccine n=1) reported a serious adverse event. The events reported were primarily hospitalizations for management of acute conditions, e.g. viral meningitis, pneumonia, reactive airways disease exacerbation, or, for pre-existing medical conditions, e.g. obstructive sleep apnea, chronic constipation, ureteropelvic junction obstruction. Dysthymic disorder was reported as a new diagnosis for one Menomune® participant.

9.0 Overview of Efficacy Across Studies:

9.1 Comparative Studies: Menactra vs. Menomune®

Efficacy was based on the demonstration of immunologic non-inferiority to Menomune®. The primary measure of immune response, in studies MTA-02 (11-18 years old) and MTA-09 (18-55 years old), was the proportion of participants achieving a four-fold or greater increase in serum bactericidal antibody, to serogroups A, C, Y, and W135. The primary hypothesis to demonstrate non-inferiority to Menomune® was achieved in both studies. The upper limit of the 95% CI, for the difference in the proportions achieving a ≥four-fold increase in SBA-BR, was less than 0.1 (i.e.10%).

For purposes of describing the overview of population responses to Menactra, immunogenicity data from study MTA-14 were also relevant. The primary objective of study MTA-14 was to evaluate lot consistency in 18-55 year old participants. Menomune® participants were enrolled for safety comparisons, and thus sera from this group was not obtained. The study design, however, did include common elements similar to studies MTA-02 and MTA-09, such as uniform serology methodology, same Menactra vaccination schedule, and identical criteria for per-protocol and modified intent-to-treat populations for immunogenicity. The three studies were conducted within a 2.5 year period, and several clinical study sites overlapped. Other measures of immune response were also provided (seroconversion, GMT, reverse cumulative distribution curve).

The per-protocol population for immunogenicity, for the three studies combined, consisted of 3186 Menactra participants and 1521 Menomune® participants.

Immunogenicity Table 1: Percentage with ≥Four-fold Increase in SBA-BR Titer (Studies MTA-02, MTA-09, MTA-14):

Serogroup	Age (years)	Menactra N=3186		Menomune® N= 1521	
		n	% with ≥4x rise in SBA-BR	n	% with ≥4x rise in SBA-BR
A	11-14	225	92.4%	225	94.7%
	15-25	1708	86.2%	791	85.3%
	26-55	1250	78.8%	505	85.5%
C	11-14	225	90.7%	225	86.7%
	15-25	1708	88.3%	791	89.4%
	26-55	1250	86.7%	505	90.7%
Y	11-14	225	82.2%	225	81.8%
	15-25	1708	77.1%	791	77.5%
	26-55	1250	72.6%	505	82.0%
W135	11-14	225	96.9%	225	96.9%
	15-25	1708	92.6%	791	95.3%
	26-55	1250	85.3%	505	92.5%

With increasing age, gradual decreases in proportions of Menactra participants with a four-fold or greater increase in SBA-BR are noted. In the corresponding age groups, the observed proportions following Menomune vaccination were more consistent.

Immunogenicity Table 2: Other immune response parameters					
	Age (years)	Menactra N= 3186		Menomune N= 1521	
		n		n	
Serogroup A					
SBA-BR GMT at Day 28	11-14	225	5677.8	225	3301.5
	15-25	1708	6799.7	791	3862.4
	26-55	1250	4244.0	505	4107.3
SBA-BR GMT at Day 0	11-14	225	106.1	225	75.6
	15-25	1708	254.8	791	171.2
	26-55	1250	192.1	505	206.9
Seroconversion rate	11-14	47	100.0	53	100.0
	15-25	242	100.0	129	99.2
	26-55	228	100.0	55	100.0
Serogroup C					
SBA-BR GMT at Day 28	11-14	225	1827.4	225	1500.4
	15-25	1708	3148.8	791	2383.2
	26-55	1250	3678.2	505	4842.7
SBA-BR GMT at Day 0	11-14	225	34.3	225	39.7
	15-25	1708	56.8	791	44.0
	26-55	1250	65.8	505	57.2
Seroconversion rate	11-14	88	100.0	81	98.8
	15-25	481	98.5	239	97.9
	26-55	345	98.0	136	98.5
Serogroup Y					
SBA-BR GMT at Day 28	11-14	225	1310.2	225	1216.8
	15-25	1708	2759.8	791	2015.9
	26-55	1250	1714.1	505	2544.0
SBA-BR GMT at Day 0	11-14	225	100.7	225	99.7
	15-25	1708	202.2	791	150.9
	26-55	1250	115.6	505	97.4
Seroconversion rate	11-14	34	100.0	31	100.0
	15-25	256	96.1	113	99.1
	26-55	296	90.2	131	95.4
Serogroup W135					
SBA-BR GMT at Day 28	11-14	225	1712.9	225	1472.9
	15-25	1708	2252.0	791	1994.9
	26-55	1250	1175.6	505	1604.1
SBA-BR GMT at Day 0	11-14	225	20.5	225	20.3
	15-25	1708	41.4	791	32.5
	26-55	1250	34.1	505	27.7
Seroconversion rate	11-14	89	97.8	86	98.8
	15-25	492	99.4	209	100.0
	26-55	467	93.2	172	98.3

N= total number of participants with valid serology data in each study
Seroconversion rate: 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.

9.2 Interference studies

In study MTA-12, Menactra was administered with Td either concomitantly or as a sequential vaccine regimen. The design of study MTA-11 was the same as MTA-12, except concomitant use with Typhim Vi® vaccine was assessed.

Menactra, when co-administered with Td vaccine, resulted in increased antibody response to the diphtheria component, increased SBA-BR GMT to each meningococcal serogroup, and comparable antibody responses to tetanus toxoid. At baseline, the diphtheria GMT in the concomitant vaccine group was 0.4 IU/ml, which increased to 120.9 IU/ml 28 days post-vaccination. Increased diphtheria antibody level reflected the high diphtheria toxoid content in Menactra (48 μg), Td vaccination, which itself contains an estimated 8 μg of diphtheria toxoid, and simultaneous administration of the two vaccines. High antibody levels to diphtheria, above that which could be explained by diphtheria content alone, suggests that diphtheria toxoid, as a carrier protein, augments the immune response to diphtheria and meningococcal components following simultaneous administration with Td. Prior Td immunization, however, resulted in a notably lower proportion of participants achieving a ≥four-fold increase in SBA-BR for serogroup C, Y and W135. The difference in the proportions achieving a ≥four-fold increase in SBA-BR antibody to serogroups C, Y and W135 was -8.8%, -20.7% and -8.7%, respectively. In the absence of a control group receiving Menactra alone in study MTA-12, it was difficult to determine if an increased meningococcal antibody response alone occurred when the two vaccines were given together, or, whether suppressed antibody responses in the group given Td prior to Menactra also occurred.

When Typhim Vi® vaccine was given first, followed by Menactra 28 days later, the observed proportion who achieved a ≥4-fold increase in SBA-BR antibody was 65.2% for serogroups Y, which was 9.3% lower compared to corresponding proportions following concomitant vaccine administration. Differences in observed proportions could be attributed to the baseline titer, which was higher for both serogroup Y, in the sequential vaccine group. Typhim Vi® vaccine and Menactra, when administered concomitantly or as a sequential regimen, do not appear to result in immunologic interference.

9.3 SBA-BR assay using baby rabbit (-BR) and human (-H) complement

Group C meningococcal antibody titers, reported from recent studies in the United Kingdom, were found to be elevated when a baby rabbit complement source was used in the bactericidal assay, relative to results using human complement. Historically, bactericidal antibody results, generated with an assay using human complement, are most closely linked with individual susceptibility to meningococcal disease, but large volumes of human sera that are a suitable source of exogenous complement are not readily available today. The sponsor was thus asked to test sera in a subset of study participants, to determine the similarity of Menactra bactericidal antibody responses compared to Menomune, when each of the complement sources was used in the assay.

Pre- and post-vaccination sera were obtained from a subset of 165 (Menactra n=84, Menomune n=81) non-randomized participants enrolled in study MTA-02 (11-18 years old), and from 100 (n=50 participants per group) MTA-09 (18-55 years old). Data, generated from an assay using each source of complement, was provided for serogroups C, Y and W135, from MTA-02 participants for whom sufficient sera were available, and likewise for serogroups Y and W135, in study MTA-09. Sera from separate subset of 102 MTA-02 participants were used for serogroup A analyses. Antibody response was assessed by reverse cumulative distribution curves, seroresponse and seroconversion rates.

Menactra and Menomune bactericidal antibody response, with each complement source, supported the same conclusion. The reverse cumulative distribution curves representing post-vaccination titers in the two vaccine groups overlapped, when either a baby rabbit or human complement source was used.

Seroresponse and seroconversion rates were also similar, as well as the immunogenicity profile in adults. Similarity of immune response for the two vaccines, with each source of complement, thus supported analyses of bactericidal antibody response using baby rabbit complement in the larger immunogenicity cohort.

Although the two assays did not correlate with each other on an individual basis, any misclassification of seroresponders occurred similarly in the two vaccine groups, and was without bias towards either Menomune or Menactra. Assay sensitivity and specificity were also not noticeably different among two populations (adolescents, adults), serogroup (A, C, Y, W135), or vaccine type (polysaccharide, conjugate). The sample size, however, was not large enough to make definite conclusions. Please see CBER statistical and clinical serology reviews for additional details.

10.0 Overview of Safety Across Studies:

The population initially sought for Menactra vaccine approval is persons aged 11-55 years old. A total of 7672 Menactra participants and 3041 Menomune® participants were enrolled in 7 studies. 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 largely in adolescents and young adults. Hence, particular attention was given to characterizing the safety profile in the 15-25 year old age group.

Overall Participant Safety Profile		
	Menactra	Menomune®
ITT population for safety*	7670 (100%)	3041 (100%)
Completed 28 day follow-up	7500 (98%)	3004 (99%)
Safety follow-up 6m post-vaccination 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

Of the seven clinical studies included in this license application, comparative safety data from studies MTA-04 and MTA-09 were most relevant, as these studies included safety hypothesis testing as a primary objective. A safety comparison was also included in studies MTA-02 and MTA-14 as a secondary objective. The four studies combined included a total of 5676 Menactra participants and 3041 Menomune® participants; 3516 and 1568 participants, respectively, were aged 15-25 years old. The four studies were conducted within a 2.5 year time period, with overlapping clinical study sites. The vaccination regimen in each of the studies, and the conduct of the safety monitoring (diary card, telephone follow-up, scripted text for long-term follow-up), was the same. The monitored safety parameters were similar in each trial, and a uniform definition was used for the intent-to-treat population for safety.

The data presented are based on a modified intent-to-treat population for safety. This population included all randomized participants, regardless of eligibility, who received a study vaccine. Participants were analyzed according to the vaccine received. If safety data was not available for a given participant or adverse event, the specified parameter was reported as missing.

10.1 Local and Systemic Adverse Events

Local Adverse Events:

15-25 years old:

For each solicited local reaction, mild and moderate reactions were reported more frequently in Menactra recipients than in Menomune® recipients (Safety Table 1). Increased local reactogenicity in Menactra participants could be attributed to the diphtheria toxoid amount contained in Menactra (48ug). Moderate pain was particularly common, and was reported approximately 4 times more by Menactra than Menomune® recipients. The majority of reactions resolved within 3 days after vaccination.

26-55 years old:

The overall rate of local adverse events was lower, compared to the 15-25 year old age group. Moderate pain was twice as frequent in Menactra participants 26-55 years old, compared with age-matched Menomune® participants (Safety Table 1). Local reactions in the Menactra group that were present during

Days 4-7, and represented continuations of reactions reported during Days 0-3, lasted an average of 5 days. A trend towards longer duration of local reactions was also observed in the Menomune® group.

Safety Table 1: Local adverse reactions (Studies (Days 0-7)

Studies MTA-02, MTA-04, MTA-09, MTA-14

		Menactra		Menomune®		Menactra		Menomune®	
		Age 15-25 years old				Age 26-55 years old			
		N= 3515		N= 1510		N=1301		N= 967	
Reaction	**Severity**	n*	%†	n*	%	n*	%†	n*	%
Redness									
	Any	435	12.4	168	10.7	148	11.4	119	12.3
< 1 inch	**Mild**	360	10.2	158	10.1	107	8.2	99	10.2
1 – 2 inches	**Moderate**	53	1.5	10	0.6	30	2.3	19	2.0
> 2 inches	**Severe**	22	0.6	0	0.0	11	0.8	1	0.1
Swelling									
	Any	388	11.0	84	5.4	143	11.0	66	6.8
< 1 inch	**Mild**	314	8.9	80	5.1	109	8.4	57	5.9
1 – 2 inches	**Moderate**	55	1.6	4	0.3	24	1.8	9	0.9
> 2 inches	**Severe**	22	0.5	0	0.0	10	0.8	0	0.0
Induration									
	Any	606	17.2	128	8.2	185	14.2	78	8.1
< 1 inch	**Mild**	508	14.5	117	7.5	140	10.8	70	7.2
1 – 2 inches	**Moderate**	87	2.5	11	0.7	34	2.6	8	0.8
> 2 inches	**Severe**	11	0.3	0	0.0	11	0.8	0	0.0
Pain									
	Any	2153	61.3	586	37.4	542	41.7	313	32.4
	Mild	1663	47.3	538	34.3	467	35.9	295	30.5
	Moderate	482	13.7	47	3.0	72	5.5	18	1.9
	Severe	8	0.2	1	0.1	3	0.2	0	0.0

*n: number of participants reporting at least one event in this category. N: total number of participants who submitted safety information at each of these time points.

†%: 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

11-55 years old:

Although severe local reactions, overall, were more frequent (1.2% vs. 0.1%) in Menactra participants, the rate was consistent with corresponding rates for other licensed vaccines.

Safety Table 3: Local adverse reactions, Days 0-7

Age 11-55 years (Studies MTA-02, MTA-04, MTA-09, MTA-14)

	Menactra		Menomune®	
	N= 5637		N= 3024	
	n	%†	n	%
At Least One Reaction	3386	60.1	1225	40.5
Severe	70	1.2	2	0.1
Redness	696	12.3	313	10.4
Severe	38	0.7	1	0.0
Swelling	650	11.5	168	5.6
Severe	35	0.6	0	0.0
Induration	936	16.6	236	7.8
Severe	26	0.5	0	0.0
Pain	3174	56.3	1059	35
Severe	12	0.2	1	0.0

*n: number of participants in each vaccine group who reported at least one solicited local reaction. N: total number of participants for whom safety information was available.
†%: n/N expressed as a percentage

Systemic Adverse Events:

15-25 years old:
The most frequent systemic reactions, in both groups, were headache (Menactra 40.3%, Menomune 36.7%) and fatigue (Menactra 34.0%, Menomune 29.8%). The occurrence of any arthralgia (20.1% vs. 13.2%) and chills (7.9% vs. 4.8%) was also common in the Menactra and Menomune® groups, respectively. The rate of severe systemic reactions, which included all rashes during the 7 day post-vaccination period, was 3.8% (135/3516) in the Menactra group and 2.5% (39/1568) in the Menomune® group. Severe malaise/fatigue and headache were most common in both groups.

26-55 years old:
In both Menactra and Menomune® participants, lower rates of any systemic reactions were observed in the 26-55 year old age group, compared to participants 15-25 year old. The average duration of headache and fatigue was extended by approximately 1 day.

Safety Table 2: Systemic adverse reactions (Studies (Days 0-7)

Studies MTA-02, MTA-04, MTA-09, MTA-14

Reaction	Severity	Menactra	Menomune®	Menactra	Menomune®
		Age 15-25 years old		Age 26-55 years old	
Headache		N= 3516	N= 1568	N= 1301	N= 968
		n*	%†	n*	%†	n*	%†	n*	%†
	Any	1418	40.3	576	36.7	487	37.4	365	37.7
	Mild	1010	28.7	443	28.3	344	26.4	266	27.5
	Moderate	374	10.6	123	7.8	135	10.4	89	9.2
	Severe	34	1.0	10	0.6	8	0.6	10	1.0
Fatigue		N= 3515	N= 1568	N= 1301	N= 968
		n*	%†	n*	%†	n*	%†	n*	%†
	Any	1196	34.0	468	29.8	379	29.1	260	26.9
	Mild	869	24.7	354	22.6	279	21.4	207	21.4
	Moderate	295	8.4	111	7.1	91	7.0	44	4.5
	Severe	32	0.9	3	0.2	9	0.7	9	0.9
Arthralgia		N= 3307	N= 1568	N= 1301	N= 968
		n*	%†	n*	%†	n*	%†	n*	%†
	Any	666	20.1	180	13.2	214	16.4	133	13.7
	Mild	504	15.2	145	10.6	167	12.8	105	10.8
	Moderate	146	4.4	33	2.4	44	3.4	26	2.7
	Severe	16	0.5	2	0.1	3	0.2	2	0.2
Chills		N= 3307	N= 1568	N= 1301	N= 967
		n*	%†	n*	%†	n*	%†	n*	%†
	Any	260	7.9	66	4.8	98	7.5	39	4.0
	Mild	190	5.7	54	4.0	78	6.0	31	3.2
	Moderate	62	1.9	12	0.9	15	1.2	6	0.6
	Severe	8	0.2	0	0.0	5	0.4	2	0.2

*n: number of participants reporting at least one event in this category. N: total number of participants who submitted safety information at each of these time points.
†%: n/N expressed as a percentage.
Headache, chills, arthralgia, fatigue: 0= none, 1= aware, easily tolerated, 2= interferes with usual activities, 3= disabling

In all age groups, grade 3 fever was not a prominent feature, and seizures did not occur in any participant. Local rash, occurring within 7 days after vaccination, was reported at or near the injection site, or described as non-specific, located more often on the extremities than on the trunk, neck or face. Generalized rash with a description consistent with hives or urticaria occurred occasionally in both groups.

Safety objectives and statistical hypotheses tested:

The endpoint used for safety comparisons was the proportion of participants with at least one severe systemic reaction during Days 0-7, and was designated either as a primary or secondary study objective in studies MTA-02, -04, -09 and –14 (Safety Table 4). Local adverse events were excluded from the endpoint definition, since the route of administration for Menactra differs from Menomune®. The definition of non-inferiority to Menomune® used for statistical hypothesis testing also varied, and reflected ongoing discussions, between CBER and the sponsor, during the course of clinical development.

Safety Table 3: Comparison of Safety Hypotheses Tested and Resultant Point Estimates

Study #	Study Objective	Hypothesis tested	% of participants with at least one severe solicited systemic reaction		Upper Limit of the CI‡
			Menactra	Menomune®	
MTA04	Primary	Upper limit of the two-sided 90% CI of the ratio of % of participants presenting at least one severe solicited systemic reaction during Days 0-7 (Menactra divided by Menomune®) is less than 3.	4.3%	2.6%	2.39
MTA09	Primary	Upper limit of the two-sided 90% (and 95%) CI of the ratio of % of participants presenting at least one severe solicited systemic reaction during Days 0-7 (Menactra divided by Menomune®) is less than 3.	3.8%	2.6%	2.12 (95% CI: 2.28)
MTA02	Secondary	Upper limit of the two-sided 90% (and 95%) CI of the difference in % of participants presenting at least one severe solicited systemic reaction during Days 0-7 (Menactra minus Menomune®) is less than 10 percentage points.	3.9%	4.1%	1.96 (95% CI: 2.37)
MTA14	Secondary	Upper limit of the two-sided 95% CI of the difference in % of 26- to 55-year-old participants presenting at least one severe solicited systemic reaction during Days 0-7 (Menactra [all consistency lots pooled] minus Menomune®) is less than 10 percentage points.	2.2%	5.5%	-1.0

‡CI: Confidence interval

All safety hypotheses were achieved. Since the nature and severity of a rash were difficult to categorize for the vaccine recipient, all rashes occurring during the first 7 days after vaccination were designated by the sponsor as a severe solicited systemic reaction, in an effort to prompt the investigator to describe additional rash characteristics. Also, for each reaction, each participant was counted no more than once. A frequency of participants reporting 2 or more severe systemic adverse events was higher in the Menactra group than the Menomune group, but the difference was not statistically significant.

Long-term follow-up 6 months after vaccination:

There was no apparent increase in the frequency of new onset asthma, diabetes mellitus or autoimmune diseases during the six months post-vaccination.

10.2 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 serious adverse event 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 vaccination. 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.

10.3 Product-Product Interactions

Concomitant vaccine administration was evaluated in two studies. In study MTA-12 (11-17 years old), Td was given simultaneously, or as a sequential regimen, with Td given 28 days prior to Menactra. Local adverse event rates at the Menactra injection site, when Menactra was given 28 days after Td, were not significantly different, compared to the rates after concomitant vaccine administration. Local reactogenicity appears to relate to the diphtheria antibody content, rather than pre-existing antibody, since local adverse event rates were not significantly different in the group given Menactra after Td vaccination. As expected, the overall frequency of systemic adverse events was increased when the Menactra and Td were given concomitantly, compared to Menactra alone (Group B, visit 2). Any arthralgia occurred in 25.1% of participants given the vaccines concomitantly, and in 12.1% of sequential vaccine group participants. Except for arthralgia, the systemic adverse event rates in the concomitant vaccine group also did not exceed rates reported for study MTA-04 Menactra participants. The safety profile of Td was not significantly different when concomitantly administered with Menactra.

Study MTA-11 (11-55 years old) implemented the same study design as MTA-12, except Typhim Vi® vaccine was used instead of Td vaccine. The overall rates of systemic adverse events increased when Menactra and Vi were given concomitantly, compared to a sequential vaccine regimen. The local adverse event profile of Menactra and Vi were not significantly changed following either vaccine regimen.

10.4 Human Reproduction Data

Two animal studies were conducted. The first study consisted of a comparative evaluation of maternal Ig transfer in rats, mice and rabbits. The second study assessed the developmental toxicology study in mice. Please refer to the review of CBER toxicologist, Dr. Hanan Ghantous.

11.0 Summary and Conclusions

The safety data from the clinical studies support the safety of Menactra in persons 11- 55 years old. The Menactra safety profile was mainly characterized by increased moderate pain compared to Menomune® recipients. Although severe local reactions, overall, were more frequent (1.2% vs. 0.1%) in the Menactra group, compared with the Menomune® group, the rate was within the limits observed for other vaccines. Headache and fatigue were also common following Menactra vaccination. A higher percentage of Menactra than Menomune® participants experienced two or more severe systemic reactions. The difference in the severe systemic reaction rates, however, was not statistically significant.

The demonstration of efficacy was inferred from non-inferiority immunogenicity comparisons to Menomune®, rather than directly observed cases of meningococcal disease. The primary measure of immune response was the proportion of participants achieving a four-fold or greater increase in serum bactericidal antibody, to serogroups A, C, Y, and W135. Functional antibody was measured with a bactericidal assay using baby rabbit complement (SBA-BR).

The difference in proportions of Menactra and Menomune® adult participants, in study MTA-09, who achieved a four-fold or greater increase in SBA-BR antibody was minimal for serogroup C (1.2%), and larger differences (4-6%) were observed for the other three serogroups. However, for serogroups A, Y and W135, the upper limit of the confidence interval for the difference in two proportions ranged from 7-9%, thus the primary hypothesis for each serogroup was achieved in this study.

Menactra and Menomune® bactericidal antibody response, with a baby rabbit or human complement source, supported the same conclusion. The reverse cumulative distribution curves representing post-vaccination titers in the two vaccine groups overlapped, when either complement source was used. Seroresponse and seroconversion rates were also similar, as well as the immunogenicity profile in adults. The relationship between SBA-BR and SBA-H results was not a linear correlation. Any misclassification of seroresponders, however, that occurred when SBA results were generated with a baby rabbit complement source appeared to be unbiased towards either the Menomune® or Menactra group. The clinical trial results, in addition to the SBA-BR/H comparisons, support demonstration of non-inferiority to Menomune® for the population.

In study MTA-12, Menactra was administered with Td either concomitantly or as a sequential vaccine regimen. Menactra, when co-administered with Td vaccine, showed increased immunologic response to the diphtheria component, and increased SBA-BR GMT to each meningococcal serogroup, and comparable antibody responses to tetanus toxoid. However, prior Td immunization, followed by Menactra 28 days later, resulted in lower proportions achieving a $\geq$4-fold increase in SBA-BR antibody were lower for serogroups C (82.4%), Y (65.1%) and W135 (87.7%), compared to concomitant vaccine administration. In the absence of a control group receiving Menactra alone in study MTA-12, it was difficult to determine if an increased meningococcal antibody response alone occurred when the two vaccines were given together, or, whether suppressed antibody responses in the group given Td prior to Menactra also occurred. Reduced immune responses to Menactra following prior Td vaccination could be due to initial expansion of diphtheria toxoid-specific B-cells, with subsequent intramolecular antigenic competition between meningococcal polysaccharide and diphtheria toxoid epitopes. This phenomenon has been observed with a meningococcal C conjugate vaccine.[14]

12.0 Recommendations

12.1 License Application

Based on the safety and immunogenicity provided, Menactra approval is recommended for the proposed indication and target population.

12.2 Post-marketing commitments

The data submitted in the Menactra biologics license application was discussed at the vaccine advisory committee meeting held on September 22, 2004. VRBPAC committee members commented on the importance of collecting additional safety data post-licensure and a need for continued evaluation of antibody persistence. Committee members also recommended the evaluation of safety and immunogenicity when Menactra is administered concurrently with other licensed vaccines given to adolescents and travelers in post-marketing studies.

12.3 Label

The package insert was revised to include comparative immunogenicity and safety data, since the proposed the approach for licensure of Menactra was based on non-inferiority comparisons to Menomune®. Of importance to clinicians, Menactra is administered intramuscularly while Menomune® is given subcutaneously. Also, the timing of Menactra revaccination has not yet been determined. The format of the label sections was also revised to be consistent with current guidelines.

13.0 Reviewer Comments

Although Menactra was demonstrated in clinical studies to be non-inferior to Menomune®, the potential additional benefits of conjugate vaccination, such as T-dependent antibody response in an infant population, affinity antibody maturation, continued antibody persistence and immunologic memory, and herd immunity have yet to be fully evaluated. Demonstration of these characteristics was not a regulatory requirement for licensure approval of a primary vaccination series in the proposed age group.

The serum bactericidal assay using baby rabbit complement, for the age group proposed in the license application, was a useful indicator of vaccine response. In a subset of study participants, Menactra and Menomune® bactericidal antibody responses assessed by reverse cumulative distribution curves, seroresponse and seroconversion rate supported the same conclusion, when either a baby rabbit or human complement source was used. A comparison of Menactra to a U.S. licensed meningococcal vaccine using SBA-BR antibody results was thus acceptable on population basis to predict similarity of vaccine effectiveness on a population basis. SBA-BR antibody results, however, were not a complete surrogate for SBA-H results, since susceptible individuals identified by each assay were not the same individuals. The relationship between SBA-BR and SBA-H results also was not a linear correlation. A threshold value that is predictive of protection, by SBA-BR antibody results, has yet to be agreed upon. Less bactericidal antibody data, generated from assays with the two complement sources, are available for serogroups other than group C.

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Appendix 1:

Vaccine Lot Information

Study Protocol #	Description	Menactra	Menomune®	Other products:
		Batch Number(s)	Batch Number(s)	Batch Number(s)
Pivotal Studies				
MTA-02	Phase II Safety + Immunogenicity	U0374AA	UA360AA	n/a
MTA-04	Phase III Safety	U0486BB	UA360AA	n/a
MTA-09	Phase III Safety + Immunogenicity	U0486BA U0486BB*	UB034AA	n/a
MTA-11	Concomitant vaccine: Typhim Vi® eval.	U0566BB	n/a	Typhim Vi®: T1053 0.9% NaCl: 1469, 1558, 1656, 2239, 2297, 2330, 2504
MTA-12	Concomitant vaccine: Td eval.	U0566BB	n/a	Td: U0521AA, U0516AA, U0519AA 0.9% NaCl: 1469, 1558, 2239, 2297
MTA-14	Lot consistency	U0566BA (Lot 1) U0567BA (Lot 2) U0568BA (Lot 3)	UB104AA	
Supplemental Studies- adults				
603-01	Phase I Dose esc, Safety + Immunogenicity	Filled vial lot #960390 Bulk lot #D01797 Label #7D71633	n/a	n/a
Animal Pharmacology and Toxicology Studies				
Study 407/128:	Comparative evaluation of maternal Ig transfer in rats, mice and rabbits	U0486BA	n/a	n/a
Study 407/158:	Developmental toxicology study in mice	U0567BA	n/a	n/a
Study 407/166:	Toxicity study to evaluate a one and two dose vaccine regimen, administered IM	U0567BA	n/a	n/a

*same batch, but labeled at different times