Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

# Australian Public Assessment Report for Groups A, C, Y and W-135 Meningococcal Polysaccharide Diphtheria Toxoid Conjugate Vaccine

Proprietary Product Name: Menactra

Sponsor: Sanofi Pasteur Pty Ltd

**August 2011**

TGA Health Safety Regulation

# About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

# About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

# Contents

# I. Introduction to Product Submission

## Submission Details

| | |
|---|---|
| *Type of Submission* | New Chemical Entity |
| *Decision:* | Approved |
| *Date of Decision:* | 19 July 2011 |
| *Active ingredient(s):* | Group A Meningococcal polysaccharide<br>Group C Meningococcal polysaccharide<br>Group Y Meningococcal polysaccharide<br>Group W-135 Meningococcal polysaccharide<br>each separately conjugated to Diphtheria Toxoid |
| *Product Name(s):* | Menactra, Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine, |
| *Sponsor's Name and Address:* | Sanofi Pasteur Pty Ltd, Locked Bag 2227, North Ryde BC NSW 1670 |
| *Dose form(s):* | Solution for Intramuscular Injection. |
| *Strength(s):* | 4 µg of each meningococcal polysaccharide conjugated to a total of approximately 48 µg of diphtheria toxoid carrier/ 0.5 ml dose |
| *Container(s):* | Vial |
| *Pack size(s):* | Five single dose vials per carton. |
| *Approved Therapeutic use:* | Menactra vaccine is indicated for active immunisation of individuals 2 through 55 years of age for the prevention of invasive meningococcal disease caused by *N meningitides* serogroups A, C, Y and W-135.<br>Menactra vaccine is not indicated for the prevention of meningitis caused by other microorganisms or for the prevention of invasive meningococcal disease caused by *N meningitides* serogroup B.<br>Menactra vaccine is not indicated for treatment of meningococcal infections.<br>Menactra vaccine is not indicated for immunisation against diphtheria. |
| *Route(s) of administration:* | Intramuscular (IM) injection |
| *Dosage:* | 0.5 mL |
| *ARTG Number (s)* | 168403 |

## Product Background

This AusPAR describes the evaluation of an application by Sanofi Pasteur Pty Ltd to register the tetravalent meningococcal vaccine, Menactra, for active immunisation in infants and adults (2-55 years). The vaccine preparation contains *Neisseria meningitidis* (*N. meningitidis*) purified polysaccharides of groups A, C, Y and W-135, each polysaccharide is individually conjugated to a detoxified purified *Corynebacterium diphtheria* toxoid. No preservative or adjuvant is added.

*N. meningitidis* is a gram-negative bacterium that causes invasive disease. The pathogen can cause epidemic disease. The two most common clinical presentations are acute bacterial meningitis and meningococcemia. Thirteen serogroups of *N. meningitidis*, based on different capsular polysaccharide structure, are known but only six serogroups (A, B, C, W-135, Y and recently X) are associated with significant pathogenic potential and are responsible for the vast majority of disease globally. Capsule is a major virulence factor of *N. meningitidis*[1]. Serogroup A *N. meningitidis* is linked to the highest incidence of meningococcal disease mainly because of the large epidemics it causes in sub-Saharan Africa and outbreaks in China, Russia, and India. Serogroup B is a major cause of endemic disease globally but prolonged outbreaks in Europe, Cuba, Brazil, in the US and in New Zealand[2]. Serogroup C is a major cause of endemic disease worldwide and since the 1990s has caused multiple case clusters and local outbreaks in the US, Canada, Latin America and Western Europe, in schools and in the community especially among adolescents and young adults[2]. It has recently emerged in China[3,4]. Serogroup W135 is a cause of sporadic disease but potentially can cause outbreaks or epidemics. The most important outbreaks associated with this serotype have been associated with Hajj pilgrimage (and secondary spread) and also significant disease in parts of the African meningitis belt[5,6,7]. Serogroup Y is a cause of endemic disease mainly in North America. It has been classically associated with pneumonia

[1]Swartley JS, Marfin AA, Edupuganti S, Liu LJ, Cieslak P, Perkins B, et al. Capsule switching of Neisseria meningitidis. Proc Natl Acad Sci U S A 1997;94(1):271-6

[2] Harrison LH. Prospects for vaccine prevention of meningococcal infection. Clin MicrobiolRev 2006;19(1):142-64.

[3] Zhang X, Shao Z, Yang E, Xu L, Xu X, Li M, et al. Molecular characterization of serogroup C Neisseria meningitidis isolated in China. J Med Microbiol 2007;56(Pt 9):1224-9

[4]Shao Z, Li W, Ren J, Liang X, Xu L, Diao B, et al. Identification of a new Neisseria meningitidis serogroup C clone from Anhui province, China. Lancet 2006;367(9508):419-23

[5] Aguilera JF, Perrocheau A, Meffre C, Hahne S. Outbreak of serogroup W135 meningococcal disease after the Hajj pilgrimage, Europe, 2000. Emerg Infect Dis 2002;8(8):761-7

[6] Lingappa JR, Al Rabeah AM, Hajjeh R, Mustafa T, Fatani A, Al Bassam T, et al. Serogroup W-135 meningococcal disease during the Hajj, 2000. Emerg Infect Dis 2003;9(6):665-71

[7] Taha MK, Giorgini D, Ducos-Galand M, Alonso JM. Continuing diversification of Neisseria meningitidis W135 as a primary cause of meningococcal disease after emergence of the serogroup in 2000. J Clin Microbiol 2004;42(9):4158-63

and the military, and infections in the elderly[2]. However, since the mid-1990s, serogroup Y strains have caused increased rates of disease in the US, Canada and Israel[8] especially among adolescents and young adults with a change in the clinical manifestations being meningitis and/or meningococcemia[2].

Meningococcal disease occurs as endemo-sporadic cases (incidence <1 per 100,000 per year), hyper-sporadic disease (1 to 10 per 100, 000 per year with localized outbreaks or case clusters occurring in regions or countries), and epidemic disease with rates ranging from 10 to 1,000 per 100,000[9]. The disease is primarily endemo-sporadic in industrialized countries and rates of meningococcal disease are highest in young children (related to waning of protective maternal antibody) with a secondary peak in adolescents and young adults aged 14.24 years (possibly related to increased transmission and acquisition of *N. meningitidis*). The main epidemiological patterns of *N. meningitidis* serogroups have been summarised in table 1 below.

[8]Rosenstein NE, Perkins BA, Stephens DS, Lefkowitz L, Cartter ML, Danila R, et al. The changing epidemiology of meningococcal disease in the United States, 1992-1996. J Infect Dis 1999;180(6):1894-901

[9] Stephens DS. Conquering the meningococcus. FEMS Microbiol Rev 2007;31(1):3-14

**Table 1: Major *N. meningitidis* serogroups and clonal complexes and associated serogroups causing disease worldwide and their epidemiological patterns.**

| Serogroup | Major associated MLST complexes | Location | Epidemiological patterns |
|---|---|---|---|
| A | ST-1, ST-5, ST-7 | Sub-Saharan Africa | Endemo-epidemic<br>Children <15 years<br>Mortality ≈15% |
| | | Russia, China, India, Northern Africa | Endemic, potential cause for outbreak<br>Children, adolescents and adults<br>Mortality ≈10%-15% |
| B | ST-32/33, ST-41/44, ST-8 | Global | Endemic, potential prolonged outbreak or hyper-sporadic incidence<br>Infants <1yr +++, children and adolescents<br>Mortality ≈8%-10% |
| C | ST-11 | Europe, The Americas | Endemo-sporadic, cluster cases and small outbreaks<br>Infants <4 yrs, adolescents +++<br>Mortality ≈10%-15% |
| W135 | ST-11 | Sub-Saharan Africa | Epidemic in Africa<br>Sporadic in other countries, potential prolonged outbreak or hyper-sporadic incidence<br>Infants and children, adolescents and young adults<br>Mortality ≈15%-20% |
| | | South Africa, Middle-East, Latin America (emerging?) | |
| Y | ST-23 | North America, Latin America (emerging?) | Endemic<br>Children and adolescents, elderly<br>Mortality ≈10% |

## Vaccination

***Polysaccharide vaccines***: The meningococcal polysaccharide vaccines were developed in the 1960's as a preventative measure to protect military recruits from acquiring invasive meningococcal disease. Following the successful field studies demonstrating the efficacy of vaccination with serogroup A and serogroup C polysaccharides, bivalent (containing serogroups A and C) and tetravalent (containing serogroups A, C, Y, and W-135) polysaccharide vaccines were licensed throughout the world in the mid-1970s and early 1980's. These vaccines are licensed for children aged ≥ 2 years, adolescents, and adults. Although the serogroup A and C polysaccharide vaccines were found to be efficacious in 87% to 89% of adults, these vaccines are not recommended for routine vaccination in young children due to limitations in the antibody response and duration of immunity. Polysaccharide vaccines are routinely administered to military recruits, and are

recommended for people at risk of meningococcal disease (including persons with terminal complement deficiencies or asplenia), for travelers to areas of high endemic and/or epidemic disease, and for students entering college (especially for those who will reside in dormitories). Polysaccharide vaccines are T-cell independent antigens that are poorly immunogenic in younger populations. These vaccines elicit disproportionately lower avidity antibodies that fail to stimulate affinity maturation and are not prone to anamnestic responses upon subsequent vaccinations.

***Conjugate vaccines:*** Conjugation of polysaccharide antigens to a protein carrier can induce T-cell dependent immune responses to the carrier protein[10], and give rise to higher antibody titres, enhanced antibody avidity, longer duration of the immune response, and immunological memory compared to unconjugated polysaccharide antigens. Serogroup C conjugate vaccines were developed to overcome the limitations of the polysaccharide vaccines by eliciting a T-cell dependent immune response. Three monovalent meningococcal serogroup C conjugate vaccines were developed and are now licensed in various countries for the prevention of serogroup C disease in adults, adolescents, children, toddlers and infants. Following the introduction of the serogroup C conjugate vaccines, there has been a marked decline in serogroup C disease. However, the variability and unpredictability of the changes in serogroup distribution noted in some geographic areas (serogroup Y disease has increased in the US and Canada and W-135 in the Middle East and South Africa) have prompted interest in extending the conjugation technology to provide coverage to these serogroups. The sponsor has used conjugation technology to develop the first tetravalent (Groups A, C, Y, and W-135) meningococcal conjugate vaccine for the protection against meningococcal disease in children, adolescents, and adults.

## Regulatory Status

The following table (Table 2) summarises the international regulatory status of Menactra.

[10]Schneerson R, Barrera O, Sutton A, Robbins JB. Preparation, characterization, and immunogenicity of Haemophilus influenzae type b polysaccharide-protein conjugates. J Exp Med. 1980;152:361-376

**Table 2. Abbreviated list of countries in which applications have been submitted and approved.**

| Country | Date of Submission | Status/ Registration Number | Health Authority Approval Date |
|---|---|---|---|
| United States (11-55 years) | 01 March 2004 | Approved 125089 | 14 January 2005 |
| Canada | 23 February 2005 | Approved 9427-S2754-42 | 03 May 2006 |
| United States (2-10 years) | 24 February 2005 | Approved | 18 October 2007 |
| United States (9-23 months) | 24 June 2010 | Approved | 22 April 2011 |
| Singapore | 21 December 2009 (Accepted for review by Health Authority 13 April 2010) | Approved SIN13922P | 24 February 2011 |

Canada: for ages 2-55 years. Note. Not a complete list of countries in which applications have been submitted and approved.

In the USA, Menactra® is indicated for active immunization of individuals 9 months through 55 years of age for the prevention of invasive meningococcal disease caused by *N. meningitidis* serogroups A, C, Y and W-135. In Canada and Singapore, Menactra® is indicated for active immunization of individuals 2 through 55 years of age.

### Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

# II. Quality Findings

## Drug Substance

There are four drug substances in this application consisting of the four conjugated polysaccharide molecules. The four conjugates consist of polysaccharides derived from *Neisseria meningitidis* serogroups A, C, W & Y, each separately covalently bound to formalin detoxified diphtheria toxin purified from *Corynebacterium diphtheriae*.

### Structure

The polysaccharide structures can be summarised as:

A. Partly O-acetylated repeat units of phosphodiester α1-6 linked N-acetylmannosamine

C. Partly O-acetylated repeat units of glycosidic α2-9 linked sialic acid

W. Partly O-acetylated alternating units of sialic acid and D-galactose linked via α2-6 and α1-6 glycosidic bonds

Y. Partly O-acetylated alternating units of sialic acid and D-glucose linked via α2-6 and α1-4 glycosidic bonds

The native polysaccharides are depolymerised to 10-25 kilo Daltons (kD) prior to conjugation. This results in chains of 25-75 monomers for serotypes A & C, and 20-50 monomers for serotypes Y & W-135.

Formaldehyde detoxification of diphtheria toxin results in cross linking estimated in the conjugates to range from 4 to 15 protein molecules.

The conjugates have a polysaccharide to protein ratio of approximately 1:1 by weight, but the majority of the polysaccharide is bound to the surface of the cross-linked protein mass. The conjugates are between 400 and 1200 kilo Daltons (kD).

These polysaccharides have been used in a number of vaccines targeted against meningococcal disease. Conjugated polysaccharide vaccines against serotype C meningococcal disease have been made using tetanus toxoid or Diphtheria $CRM_{197}$ protein.

**Manufacture**

The four polysaccharides are manufactured by extraction and purification of the polysaccharide from each of four serotypes of *Neisseria meningitidis*. Strains are cultured, inactivated and the polysaccharides recovered using a series of purification steps. The diphtheria toxoid carrier protein is extracted from *Corynebacterium diphtheriae* and detoxified using formaldehyde.

The polysaccharides are then hydrolysed and sized, before being covalently linked to the carrier protein via an adipic acid dihydrazide link to the carboxyl groups on the toxoid.

Seed banking processes are satisfactory. A new seed bank has recently been constructed for two of the four polysaccharide production strains. These new banks have recently been approved for use in the unconjugated tetravalent polysaccharide vaccine Menomune.

There are no issues of concern related to viral safety or transmissible spongiform encephalopathies (TSE), and the use of material derived from human or animal sources has been kept to a minimum.

**Physical and Chemical Properties**

The physical and chemical properties of the drug substances are similar to those of other conjugated polysaccharide vaccines. The drug substances are designed to induce an immune response in the individual, to the four serotypes of *N. meningitidis* included in the vaccine.

**Specifications**

The proposed specifications, which control identity, content, potency, purity and other biological and physical properties of the drug substances relevant to the dose form and its intended clinical use, were in large justified and appropriate. Validation data were submitted in support of the test procedures.

### Stability

Stability data for the polysaccharide and protein bulks have been generated at -60°C to -80°C for up to 36 months. These data show no evidence of instability or degradation. The data submitted support a shelf life of 36 months at -60°C to -80°C.

## Drug Product

### Formulation(s)

The Menactra dosage form is a sterile, aqueous solution that contains four group-specific polysaccharide antigens from *Neisseria meningitidis* separately conjugated to Diphtheria Toxoid protein. Each 0.5 ml single dose is formulated to contain 4 µg of each meningococcal polysaccharides conjugated to a total of approximately 48 µg of Diphtheria Toxoid carrier.

Excipients included in the drug product are sodium chloride, sodium phosphate, dibasic, anhydrous and sodium phosphate and monobasic, monohydrate.

The preparation is not adjuvanted and does not contain antimicrobial preservatives. The vaccine contains no thiomersal.

### Specifications

Most of the specifications which control identity, potency, purity, dose delivery and other physical, chemical and microbiological properties relevant to the clinical use of the product were justified and appropriate validation data have been submitted in support of the test procedures.

### Stability

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. An overview of the stability studies performed and additional data submitted during the evaluation support a proposed shelf life for the filled vials of 24 months from the date of filling when stored at 2-8°C. All questions put to the company regarding aspects of the stability data were resolved during the evaluation process.

## Biopharmaceutics

Biopharmaceutic data are not required for this product.

## Quality Summary and Conclusions

The administrative, product usage, chemical, pharmaceutical, microbiological and biopharmaceutic data (as applicable) submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

### Issues of concern

A number of issues requiring resolution before the product could be recommended for approval were identified during the evaluation of sterility aspects and the evaluation of manufacturing and quality control aspects and were referred to the sponsor for comment or resolution. A Pharmaceutical Sub-Committee review supported the need for these issues to be satisfactorily resolved before approval and also raised further concerns that required confirmation. The sponsor responded to all quality issues raised and satisfactory resolutions to all issues were reached.

# III. Nonclinical Findings

## Introduction

The nonclinical part of the current Australian submission was generally acceptable and in accordance with the European Medicines Agency (EMA) guideline on the nonclinical pharmacological and toxicological testing of vaccines[11]. Nonclinical studies with Menactra consisted of immunogenicity studies in rodents that were not Good Laboratory Practice (GLP) compliant, and GLP compliant combined acute and repeat dose toxicity study in rats, an antibody transfer study in mice, rats and rabbits and embryofetal development toxicity study in mice. No safety pharmacology or local tolerance studies were conducted and some toxicology study deficiencies were however noted.

## Pharmacology

### Primary pharmacology

Immunogenicity studies in mice and rats showed that the conjugated tetravalent vaccine (Menactra) induced substantial immunogenic responses to all four serogroup polysaccharides, with high antibody titres relative to the unconjugated formulations. Addition of adjuvant generally increased immunogenic responses, although only slightly in the majority of studies. While immunisation with a single dose of Menactra induced only a low level of anti-polysaccharide antibodies, this primary antibody response increased significantly upon immunisation with a second and/or third dose. A 0.25 µg subcutaneous (SC) dose given to mice twice at a 14 day interval was the optimised dosing regimen for immunogenic responses. Serum bactericidal activity was also observed against meningococcal A, C, Y and W-135 conjugate antigens at this optimised dosing regimen in mice. This optimal dose in mice (0.25 µg/serogroup polysaccharide) represented one-sixteenth of the proposed clinical dose (10-fold the proposed clinical dose based on BSA; Mouse dose = 0.25 µg/28 g = 8.93 µg/kg = 27 µg/$m^2$; Human dose = 4 µg/50 kg = 0.08 µg/kg = 2.6 µg/$m^2$).

Immunogenicity studies, primarily performed in mice, were conducted with the SC route, not the clinical IM route, due to dose volume limitations. However, taking into account dose and potential strain differences, the mouse and rat antibody titre responses to IM Menactra in toxicity studies were broadly within the range observed in the rodent SC immunogenicity studies, and hence the SC data are probably relevant to IM administration.

No nonclinical protective efficacy studies were submitted for Menactra, as *N. meningitidis* only infects humans, and there are no suitable animal models of *N. meningitidis* infection. However, sera taken from mice given Menactra (at 0.25 µg/serogroup polysaccharide SC dose) showed bactericidal antibody titres against all four *N. meningitidis* serogroups. As a comparative study with currently registered tetravalent polysaccharide vaccines was not performed, it is difficult to interpret the relevance of the demonstrated rodent immune responses in the clinical setting.

[11] Note for guidance on preclinical pharmacological and toxicological testing of vaccines. CPMP/SWP/465/95. http://www.tga.gov.au/pdf/euguide/swp046595en.pdf

### Secondary and safety pharmacology

No dedicated secondary or safety pharmacology studies have been conducted with Menactra. However, no remarkable central nervous system (CNS), respiratory, cardiovascular or gastrointestinal effects were observed in the rat IM repeat dose toxicity study at clinical Menactra doses.

## Toxicology

### Acute and repeat-dose toxicity

A combined GLP compliant single and repeat dose IM toxicity study was performed in Sprague-Dawley rats. Rats were considered a suitable animal model based on their demonstrated immunogenic responses and feasibility for administering the clinical IM dose. Study deficiencies included low animal numbers and limited organ weight sampling, but this is unlikely to significantly alter study outcomes.

There was no remarkable evidence of systemic toxicity following a single or two IM injections of Menactra. Findings were generally limited to changes in white blood cell parameters, particularly neutrophil counts, which are considered a pharmacological rather than toxicological effect, and local inflammatory changes at the injection site observed the day after dosing, which resolved after a two week recovery period.

The 0.5 mL IM dose administered to rats (over two injection sites) was equivalent to that proposed clinically, and when corrected for body surface area (BSA) represented a >30-fold clinical safety margin (36-fold rat to human safety margin; Rat dose = 4 µg/250 g = 16 µg/kg x 6 = 96 µg/$m^2$; Human dose = 4 µg/50 kg = 0.08 µg/kg = 2.6 µg/$m^2$). It should be noted that negligible serogroup specific antibody responses were observed after a single dose in this study, while significant antibody exposure was demonstrated after two doses. Thus, acute toxicity may not have been adequately assessed in this study, based on the limited antibody response and exposure following a single dose. However, most importantly, two doses of Menactra, equivalent to that proposed clinically, were not associated with any remarkable adverse effects.

### Genotoxicity and carcinogenicity

No genotoxicity or carcinogenicity studies were submitted for Menactra. This is considered acceptable for a conventional vaccine[12]

### Reproductive toxicity

It is proposed to administer Menactra to adults, including women of childbearing age, and there is also potential for administration of the vaccine to pregnant women. No study of fertility was submitted, and such studies are usually not necessary for a new vaccine[12]. No effects on mating performance or fertility were reported in the definitive mouse embryofetal development study following administration of a 0.8 µg IM Menactra dose (at one fifth of the clinical dose) two weeks prior to mating. However it is unclear whether a single IM dose prior to mating would result in adequate dam exposure to the vaccine for assessment of fertility effects.

[12] CPMP/SWP/465/95 Note for guidance on preclinical pharmacological and toxicological testing of vaccines.
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004004.pdf

The GLP compliant mouse embryofetal toxicity study of Menactra showed no remarkable maternal, fetal or pup effects following an IM dose of 0.8 µg (at one fifth of the clinical dose; 33-fold clinical dose based on BA; mouse dose = 0.8 µg/28 g = 28.6 µg/kg x 3 = 86 µg/$m^2$; human dose = 2.6 µg/$m^2$) to the dams two weeks prior to mating and on gestation days 6 and/or 18. This study was adequately conducted in terms of animal model, numbers, maximum feasible IM dose and parameters investigated. Importantly, antibody transfer was not examined in this study, however antibody exposure was demonstrated in dams, pups and fetuses in mice administered Menactra under an identical treatment protocol in a separate study. In this antibody transfer study, mice were given an identical IM dose of 0.8 µg, while rats and rabbits were given the clinical IM dose of 4 µg two weeks prior to mating and on gestation days 6 and/or 18, 20 or 29, respectively. This study also examined aspects of reproductive toxicity for the three species. However, no definitive conclusions could be drawn regarding potential reproductive effects given the absence of control animals, low (6-8) animal numbers in each group and inconsistencies observed.

No adequate studies examining antibody excretion in animal milk were provided. Careful consideration of the risks and benefits of vaccination are recommended should Menactra be given to nursing mothers.

**Use in children**

No dedicated toxicology studies have been conducted in juvenile or young animals with Menactra. However, there were no nonclinical findings indicating any target organ or systemic toxicity relevant for developing systems, possible effects on growth and/or development in the intended age group or pharmacological effect of the test compound that would affect developing organ(s) and warrant the use of toxicity studies in juvenile animals[13]. Moreover, when corrected for BSA, the clinical dose safety margin in a 2 year old child (4 µg/0.5 $m^2$ = 8 µg/$m^2$) is still ≥10-fold that given to mice (86 µg/$m^2$) and rats (96 µg/$m^2$) in toxicity studies without any remarkable adverse effects.

There were also no immunogenicity studies in neonatal or young animals. Although the relative importance of B and T cells in responses to Menactra were not directly investigated in animals, the induction of high antibody titres, and a mnemonic response in rodents suggested that an appropriate T-cell dependent response was induced, as required for immunisation of human infants.

**Local tolerance**

No conventional GLP-compliant local tolerance studies were submitted for Menactra. However, local tolerance investigations were performed as part of the acute and repeat dose IM rat toxicity study. Local reactions in rats given two clinical IM doses of Menactra were generally restricted to inflammatory changes at the injection site observed the day after dosing. Although the local changes were also seen in control animals, these were slightly increased in the treated groups but were reversible after a two week post-dose period. This dose was equivalent to that proposed clinically, and when corrected for BSA, represented a >30-fold clinical safety margin.

[13] Guideline on the need for Non-Clinical Testing in Juvenile Animals of Pharmaceuticals for Paediatric Indications. EMEA/CHMP/SWP/169215/2005. http://www.tga.gov.au/pdf/euguide/swp16921505en.pdf

## Nonclinical Summary and Conclusions

- Nonclinical data consisted of immunogenicity studies in rodents, a combined acute and repeat dose toxicity study in rats, an antibody transfer study in mice, rats and rabbits and an embryofetal development toxicity study in mice. The current Australian nonclinical submission was generally acceptable for a conventional vaccine; however some data and study deficiencies were noted.
- Immunogenicity studies in mice, and rats showed substantial serum antibody titres and serum bactericidal activity (SBA) against meningococcal A, C, Y and W-135 conjugate antigens following a 2 or 3 dose immunisation protocol with Menactra (≥0.25 µg/serogroup polysaccharide/dose; one-sixteenth of the proposed clinical dose).
- No nonclinical protective efficacy studies were performed.
- No secondary or safety pharmacology studies were performed.
- There was no remarkable evidence of systemic toxicity in rats given a single or two IM injections of Menactra. This dose was equivalent to that proposed clinically, and when corrected for body surface area (BSA), represented a >30-fold clinical safety margin.
- Local reactions following a single or two IM injections of Menactra in rats one day after injection were generally restricted to a slight inflammatory response and were resolved after a two-week recovery period.
- No genotoxicity or carcinogenicity studies were submitted. This is acceptable for this type of product.
- In mice given a single IM dose of Menactra (at one fifth of the clinical dose; >30-fold clinical dose based on BSA) two weeks prior to mating and on gestation days 6 and/or 18, no significant maternal, fetal or pup toxic effects were observed. Antibody transfer was not examined in this study. No adequate studies examining antibody excretion in animal milk were provided.

### Recommendations

Nonclinical studies for Menactra demonstrated substantial immunogenicity and bactericidal activity of the conjugate vaccine in mice and rats. While no nonclinical protective efficacy studies were submitted, there are no suitable animal models of *N. meningitidis* infection. Therefore, the demonstration of protective efficacy will rely on clinical data.

No remarkable systemic or local effects were observed in rats given the clinical IM Menactra dose on two occasions.

No remarkable concerns were raised in relation to effects on embryofetal development in mice, supporting its use in woman of childbearing age.

The lack of dedicated safety pharmacology and local tolerance studies is not considered a major deficiency, given major organ systems and local effects were examined in the rat IM repeat dose toxicity study.

There are no objections on nonclinical grounds to the registration of Menactra vaccine provided satisfactory investigation of efficacy and local effects are demonstrated in clinical studies.

The Product Information should be amended as indicated.

# IV. Clinical Findings

## Introduction

The clinical development program for Menactra vaccine started in July 1997. A dose-escalation study (Study 603-01, Stage I, II, and III) was conducted in the US. In this dose-escalating study using 1 µg, 4 µg, and 10 µg of each conjugated polysaccharide per dose, a single dose of Menactra vaccine was administered to adults (Stage I), two doses were administered to toddlers (1 to 2 years of age) in two-month intervals (Stage II), and three doses were administered to infants at 2, 4, and 6 months of age (Stage III). Based on the safety and immunogenicity results from the dose escalation studies, as well as the information obtained from the precursor bivalent A/C studies, the sponsor decided to evaluate further the 4 µg conjugated polysaccharide dosage formulation in children, adolescents, and adults.

Data from 11 clinical studies constitute the primary clinical data in this submission.

### Phase I. Dose-Escalation Study

***Study 603-01*** (Stages I, II, and III) was a randomized, dose-escalation study conducted in the US in three age groups (adults, toddlers aged 1 to 2 years, and infants aged 2, 4, and 6 months). Only the results from the adult Stage I of Study 603-01 are included in this CTD application**.**

### Phase II. Comparative and Concomitant Vaccine Studies

#### *1) Adults*

*a) Study MTA09* was a randomized, modified double-blind, comparative safety, and immunogenicity study conducted in the US in healthy adults aged 18 to 55 years. The primary objective of this study was to describe and compare the antibody response and safety profile following one dose of Menactra vaccine to one dose of the licensed polysaccharide vaccine, Menomune®-A/C/Y/W-135.

*b) Study MTA11* was a randomized, modified double-blind, safety and immunogenicity study of Menactra vaccine administered alone or concomitantly with the licensed Typhim Vi vaccine conducted in the US in healthy adults aged 18 to 55 years. There were two primary objectives in this study. The first objective was to compare the antibody responses to one dose of Typhim Vi vaccine when administered with placebo or with Menactra vaccine. The second objective was to compare the percent 4-fold rise in serum bactericidal antibody responses to each of the four serogroups in Menactra vaccine 28 days post-vaccination when administered concomitantly with Typhim Vi vaccine or 28 days after Typhim Vi vaccine.

#### *2) Adolescents*

*a) Study MTA02* was a randomized, modified double-blind, comparative safety, and immunogenicity study conducted in the US in healthy adolescents aged 11 to 18 years. The primary objective of this study was to describe and compare the antibody response and

safety profile following administration of one dose of Menactra vaccine or to one dose of the licensed Menomune vaccine.

*b) Study MTA12* was a randomized, modified double-blind, safety and immunogenicity study of Menactra vaccine administered concomitantly or one month after the licensed tetanus/diphtheria (Td) vaccine conducted in the US in healthy adolescents aged 11 to 17 years. There were two primary objectives in this study. The first objective was to describe and compare the percent 4-fold rise in serum bactericidal assay using baby rabbit complement (SBA-BR) antibody responses to each of the four serogroups following administration of Menactra vaccine in the two study groups 28 days post-vaccination. The second objective was to describe and compare the diphtheria and tetanus booster response rates when a tetanus-diphtheria (Td) vaccine was administered alone or concomitantly with Menactra vaccine.

### *3) Children*

*a) Study 603-02* was a randomized, modified double-blind, comparative safety, and immunogenicity study conducted in the US in healthy children aged 2 to 10 years. The primary objective of this study was to describe and compare the antibody response and safety profile following one dose of Menactra vaccine to one dose of the licensed Menomune vaccine.

b*) Study MTA15* was a randomized, comparative safety and immunogenicity study conducted in the United Kingdom (UK) in healthy children aged 2 to 5 years. The primary purpose of this study was to describe and compare the percent 4-fold rise in SBA antibody responses to the serogroup C conjugated polysaccharide in Menactra vaccine versus a group of age matched children who received a dose of *Haemophilus influenzae* type B conjugate vaccine. Both study groups had been previously vaccinated with a monovalent serogroup C conjugate vaccine in their first year of life.

*c) Study MTA17 Stage I* was a randomized, comparative immunogenicity study conducted in the US in healthy children aged 3 to 5 years. The primary purpose of this study was to describe the antibody response following a reduced challenge dose (1/10) of Menomune vaccine in children who had received a single dose of Menactra vaccine approximately 2 years earlier compared to an age-matched group of children who had no previous experience with meningococcal vaccines (vaccine-naïve Control group).

**Phase III Large Scale Safety and Manufacturing Lot Consistency Studies**

### *1) Adults*

*Study MTA14* was a randomized, comparative safety and immunogenicity study conducted in the US in healthy adults aged 18 to 55 years. The primary objective of this study was to compare the antibody response group mean SBA-BR titres (geometric mean titres [GMTs]) 28 days after vaccination to three consecutive lots of Menactra vaccine. A comparative safety study to the licensed tetravalent polysaccharide Menomune vaccine in 26 to 55 year-old participants was conducted within Study MTA14.

### *2) Adolescents*

*Study MTA04* was a randomized, comparative safety study conducted in the US in healthy adolescents aged 11 to 18 years. The primary objective of this study was to compare the safety profile of participants who received one dose of Menactra vaccine to those who received one dose of the licensed Menomune vaccine.

### *3) Children*

*Study MTA08* was a randomized, comparative safety study conducted in the US and in Chile in healthy children aged 2 to 10 years. The primary objective of this study was to compare the safety profile in participants who received one dose of Menactra vaccine to those who received one dose of Menomune vaccine. The immune responses to both vaccines were evaluated for exploratory purposes only in a subset of the Chilean participants. Table 3 summarizes the design and size of the 11 studies included in this application.

**Table 3: Design and Size of the Clinical Studies Included in this submission (Table continued across two pages).**

| Study | Type of Study | Vaccination Schedule | Age of Population (yrs) | Safety Population | | |
|---|---|---|---|---|---|---|
| | | | | Menactra Vaccine | Menomune Vaccine | Other |
| 603-01 Stage I | Dose escalation | 1 vaccination (Day 0) | 18 to 55 | 30* | None | NA |
| MTA09 | Safety and immunogenicity comparison of Menactra vaccine versus Menomune vaccine | 1 vaccination (Day 0) | 18 to 55 | 1384 | 1170 | |
| MTA14 | Consistency of immunogenicity of Menactra vaccine and safety comparison of Menactra vaccine versus Menomune vaccine | 1 vaccination (Day 0) | 18 to 55 | 1582 | 458 | NA |
| MTA11 | Safety and immunogenicity of concomitant administration of Menactra vaccine with Typhim Vi Vaccine | 2 vaccinations<br>Group A: Vi + Menactra vaccine (Day 0) and Placebo (Day 28)<br>Group B: Vi + Placebo (Day 0) and Menactra vaccine (Day 28) | 18 to 55 | 945<br>469<br>476 | None | NA |
| Total Adults | | | | 3941 | 1628 | NA |

| Study | Type of Study | Vaccination Schedule | Age of Population (yrs) | Safety Population | | |
|---|---|---|---|---|---|---|
| | | | | Menactra Vaccine | Menomune Vaccine | Other |
| 603-02 | Safety and immunogenicity comparison of Menactra vaccine versus Menomune vaccine | 1 vaccination (Day 0) | 2 to 10 | **696** | **702** | **NA** |
| MTA08 | Safety comparison of Menactra vaccine versus Menomune vaccine | 1 vaccination (Day 0) | 2 to 10 | **1712** | **1519** | **NA** |
| MTA15 | Immunogenicity comparison of Menactra vaccine versus Hib vaccine in meningococcal vaccination experienced subjects | 1 vaccination (Day 0) | 2 to 5 | **52** | **NA** | **50 (Hib vaccine)** |
| MTA17 Stage I | Evaluation of immune memory in subjects previously vaccinated with Menactra vaccine | 1 vaccination (Day 0) (reduced dose [1/10] Menomune vaccine) | 3 to 5 | **71**** | **NA** | **100** |
| | | | **Total children** | **2460** | **2221** | |
| **Total for all studies** | | | | **10,130** | **5262** | |
| MTA02 | Safety and immunogenicity comparison of Menactra vaccine versus Menomune vaccine | 1 vaccination (Day 0) | 11 to 18 | **440** | **441** | **NA** |
| MTA04 | Safety comparison of Menactra vaccine versus Menomune vaccine | 1 vaccination (Day 0) | 11 to 18 | **2270** | **972** | **NA** |
| MTA12 | Safety and immunogenicity of concomitant administration of Menactra vaccine with Tetanus and Diphtheria Combined vaccine | 2 vaccinations<br>Group A: Td vaccine + Menactra vaccine (Day 0) and Placebo (Day 28)<br>Group B: Td vaccine + Placebo (Day 0) and Menactra vaccine (Day 28) | 11 to 17 | **1019**<br>507<br>512 | **None** | **NA** |
| | | | **Total Adolescents** | **3,729** | **1413** | **NA** |

* Two groups of 30 adult participants received either a 1 µg dose or a 10 µg dose of Menactra vaccine during Stage I.

** These subjects are not included in the total for all studies since they were already enrolled in Study 603-02.

### Good Clinical Practice Aspects

The clinical studies conducted in the US, Chile, and UK and summarised in this application were conducted in accordance with the current Good Clinical Practices (cGCPs).

## Pharmacokinetics

Due to the nature of the product (polysaccharide diphtheria toxoid conjugated vaccine), its composition (amount of active substance in the injected dose and absence of adjuvant), and the route of administration (intra-muscular injection), information relative to the bioavailability of the product's components following administration have not been compiled.

## Pharmacodynamics

### Introduction

The primary assay used for measuring the immune responses to Menactra vaccine was SBA-BR (baby rabbit as the exogenous source of complement). This assay determines the level of complement-mediated killing of the target bacteria, *N. meningitidis* serogroups A, C, Y and W-135. The assay was validated for precision, dilutability (linearity), specificity, and limit of detection in one laboratory. Prior to evaluation of the clinical samples in a second laboratory, the assay was assessed for accuracy (equivalency to the established assay) and reassessed for precision. In addition to measuring antibody responses to Menactra vaccine by SBA-BR, the secondary assays used for the quantitation of anti-polysaccharide antibodies Immunoglobulin G (IgG) and IgM to *N meningitides* serogroups A, C, Y, and W-135 included the enzyme-linked immunosorbent assays (ELISA). The ELISA IgG assay was validated for precision, specificity, dilutability (linearity), limit of detection, lower limit of quantitation, and range in one laboratory and then transferred to a second laboratory.

The techniques for assessment of meningococcal vaccines are based on World Health Organization (WHO) recommendations (see below). In November 2000 to address the results of the comparative study and to consider the available information coming from the introduction of serogroup C meningococcal conjugate vaccines in the UK, an independent expert panel unanimously agreed to the following recommendations regarding the use of the SBA-BR in the development of serogroup C conjugate vaccines[14]:

• SBA-BR titres < 1:8 indicate an absence of protection;

• SBA-BR titres ≥ 1:128 correlate with the established bactericidal protective response of

≥ 1:4 obtained when using human complement in the assay; and

• SBA-BR titres in the equivocal zone (1:8, 1:16, 1:32, 1:64) should be reassessed with human complement in the assay.

[14]Jodar L, Stephens D, Feavers IM. Assay parameters and methods of data analysis for the comparison of complement sources in the Neisseria meningitidis serogroup C serum bactericidal assay. Biologicals. 2002; 30:323-329

***SBA-BR:*** The assay performed by the sponsor follows the current requirements and recommendations for assessing the immune responses to meningococcal polysaccharide vaccines.

• The SP SBA-BR assay conforms to the 1976 requirement prescribed by the WHO Expert Committee on Biological Standardization for demonstrating the induction of bactericidal antibody production in healthy adult subjects immunized with meningococcal vaccines against *N. meningitidis* serogroups A, C, Y, and W-135[15], [16].

• The SP SBA-BR correlated favorably with the Centers for Disease Control and Prevention (CDC) SBA-BR in an international comparison study to establish parameters for standardization. The SP SBA-BR continues to utilize the same reference standard, CDC donor R21654-3430107, that was one of the quality control serum samples in the comparison study[17].

• The SP SBA-BR was performed according to an adaptation of the standardized CDC method recommended by the WHO Expert Committee of the Department of Vaccines and Biologicals as the optimal methodology[18].

**Association between SBA-BR data and SBA-HC data generated by SP**

In order to qualify the immunological relevance of the results obtained by the SBA-BR and generated during the Menactra vaccine clinical development program, additional bactericidal testing was performed on three sera panels to assess the association between bactericidal antibody titres measured by SBA-BR and human complement (SBA-HC).

The three sera panels originated from subjects enrolled in the following two studies:

- Study MTA02, adolescents aged 11 to 18 years, sera from subjects who received Menactra vaccine (N=50 to 84) or Menomune vaccine (N=52 to 81) were used for evaluation of serum bactericidal antibody responses to A, C, Y, and W-135 serogroups.
- Study MTA09, adults aged 18 to 55 years, sera from subjects who received Menactra vaccine (N=50) or Menomune vaccine (N=50) were used for evaluation of serum bactericidal antibody responses to Y and W-135 serogroups.

[15]World Health Organization Expert Committee on Biological Standardization: Twenty seventh Report. WHO Tech Rep Ser. 1976;594:1-86

[16]World Health Organization Expert Committee on Biological Standardization: Thirty-first report. WHO Rep Ser. 1981:658:174-183

[17] Maslanka SE, Gheesling LL, Libutti DE, et al. Standardization and a multilaboratory comparison of Neisseria meningitidis serogroup A and C serum bactericidal assays. The multilaboratory study group. Clin Diagn Lab Immunol. 1997;4(2):156-167

[18] Jodar L, Cartwright K, Feavers IM. Standardisation and validation of serological assays for the evaluation of immune responses to Neisseria meningitidis serogroup A and C vaccines. Biologicals. 2000;28:193-197

- Study 603-02 children aged 2-3 years, sera from subjects who received Menactra vaccine (N=52) or Menomune vaccine (N=53) and children aged 4-10 years (N= 84 for both Menactra and Menomune) were used for evaluation of serum bactericidal antibody responses to A, C, Y and W-135 serogroups.

The response rates measured by the percent ≥ 4-fold rise in SBA-BR titres were in close agreement to the proportion of subjects that had post-vaccination titres at or above the protective level of 1:4 using human complement for serogroup C, and were at or above the putative protective level of 1:4 using human complement for serogroups A, Y, and W-135. The close agreement between the percent ≥ 4-fold rise in SBA-BR and the proportion of subjects having post-vaccination SBA-HC titres ≥ 1:4 provides strong support that the SBA-BR can be used for assessing the non-inferiority between Menactra vaccine and Menomune vaccine for each of the four serogroups.

### Primary pharmacology

The sponsor's pharmacology studies are listed in Table 4 below.

**Table 4: Listing of Clinical Pharmacology Studies**

| Study Identifier | Location of Study Report in CTD | Objective(s) of the Study | Study design and Type of Control | Test Product(s); Dosage regimen; Route of administration | Number of subjects | Country(ies); Trial period (FVFS – LVLS*) | Healthy Subjects or Diagnosis of Patients | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| 603-01<br>Stage I | 5.3.4.1 | **Primary**: Safety, reactogenicity and dose-escalation response of Menactra vaccine in adults | Open-label, uncontrolled, dose-escalating study | Menactra vaccine<br>**Dose**: 1, 4, or 10 µg polysaccharide per serogroup<br>One injection on D0.<br>**Route**: Intramuscular | 90 | US<br>July 7, 1997 to October 2, 1997 | Healthy adults aged 18 to 55 years | Completed. Final |

* FVFS= First visit of the first subject. LVLS= last visit of the last subject.

### *Phase I Dose Escalation Study 603-01*

Study 603-01 Stage I was a Phase I, unblinded, open-label, dose-escalation study conducted in the US (as shown in Table 4). A total of 90 healthy adults (aged 18 to 55 years) were enrolled to receive a single injection of one of three different formulations (30 participants per dosage formulation) of the investigational product. Participants were monitored for immediate adverse reactions for 30 minutes following vaccine administration. On the evening of, and for 3 days following vaccine administration, adults were asked to record on pre-printed diary cards their highest temperature (measured orally) for each day, as well as the presence and severity of solicited local and systemic reactions. Participants returned their completed diary card to the study site at the Day 4 visit and the diary cards were kept with the study records. Safety was evaluated at each visit by interview to detect intercurrent illness, unreported events, severe or unexpected adverse events, and any hospitalization. Blood samples (10 mL whole blood) were collected by venipuncture prior to vaccination on Day 0 and 28 to 30 days after vaccination. Sera from the blood samples were used to perform serologic assays for antibodies to meningococcal serogroups A, C, Y, and W-135 capsular polysaccharides. Additional blood (approximately 20 mL) and urine specimens were collected prior to vaccination on Day 0, on Day 4, and on Days 28 to 30 after vaccination for evaluation of toxicity by a complete blood count (CBC), serum chemistry analyses (serum aspartate transaminase (AST), alanine transaminase (ALT), blood urea nitrogen [BUN], creatinine, and glucose), and urinalysis.

*Response to meningococcal polysaccharides (per-protocol population)*

Antibody responses to the three dosage formulations of Menactra vaccine were assessed. SBA-BR and IgG enzyme linked immunosorbent assay (ELISA) were used to measure anti-polysaccharide antibodies in the Day 0 pre-vaccination and in the Day 8 post-vaccination serum samples.

The immunogenicity results from this study are summarised in Table 5.

**Table 5: Study 603-01, Stage I (Adults): SBA-BR and IgG ELISA Titers at Baseline and at Day 28 Post-Injection, by Menactra Vaccine Dosage Level (Per-Protocol Population)**

| Serogroup/ Dosage Level | $N_{Day0}/N_{Day28}$ | Proportion with SBA-BR ≥ 1:8 | | SBA-BR GMT (95% CI*) | | IgG ELISA GMC (95% CI*) | |
|---|---|---|---|---|---|---|---|
| | | Day 0† | Day 28‡ | Day 0† | Day 28‡ | Day 0† | Day 28‡ |
| **Serogroup A** | | | | | | | |
| 1 µg | 26/26 | 96.2 | 100.0 | 460.2 (223.0-949.7) | 3054.9 (1872.9-4982.9) | 3.4 (1.8-6.6) | 19.4 (11.6-32.3) |
| 4 µg | 28/28 | 92.9 | 100.0 | 487.3 (231.2-1027.2) | 6720.2 (4666.5-9677.7) | 3.3 (2.3-4.8) | 38.4 (22.2-66.4) |
| 10 µg | 27/27 | 100.0 | 100.0 | 525.3 (286.6-962.9) | 10865.1 (7651.5-15428.2) | 3.1 (1.7-5.6) | 56.4 (31.8-99.9) |
| **Serogroup C** | | | | | | | |
| 1 µg | 26/26 | 42.3 | 88.5 | 20.9 (8.8-49.6) | 540.0 (238.1-1224.7) | 0.3 (0.2-0.5) | 2.2 (1.2-4.1) |
| 4 µg | 28/28 | 35.7 | 100.0 | 16.4 (7.1-37.7) | 1559.8 (799.9-3041.5) | 0.4 (0.2-0.7) | 5.5 (3.0-10.1) |
| 10 µg | 27/27 | 37.0 | 100.0 | 19.2 (8.0-45.8) | 1755.6 (880.5-3500.4) | 0.5 (0.3-0.9) | 11.1 (5.5-22.5) |
| **Serogroup Y** | | | | | | | |
| 1 µg | 26/26 | 42.3 | 84.6 | 9.4 (5.9-14.9) | 95.5 (40.5-225.0) | 0.6 (0.4-1.0) | 2.8 (1.5-5.2) |
| 4 µg | 28/28 | 46.4 | 89.3 | 19.0 (8.8-41.2) | 390.0 (143.3-1061.3) | 1.3 (0.7-2.5) | 6.8 (3.2-14.6) |
| 10 µg | 27/27 | 63.0 | 88.9 | 28.1 (12.9-61.6) | 386.0 (145.2-1026.2) | 1.0 (0.5-2.1) | 7.7 (3.4-17.2) |
| **Serogroup W-135** | | | | | | | |
| 1 µg | 26/26 | 30.8 | 88.5 | 13.6 (5.7-32.4) | 498.5 (203.2-1223.2) | 0.5 (0.3-0.9) | 2.3 (1.0-5.3) |
| 4 µg | 28/28 | 53.6 | 85.7 | 10.0 (5.9-16.9) | 608.9 (250.3-1480.9) | 0.6 (0.3-1.0) | 5.8 (2.9-11.7) |
| 10 µg | 27/27 | 29.6 | 100.0 | 9.8 (5.0-19.1) | 1848.1 (1075.4-3176.2) | 0.4 (0.2-0.7) | 9.3 (4.8-18.1) |

* CI: Confidence Interval; Day 0: Baseline blood sample drawn prior to vaccination; Day 28: Blood sample drawn 28 days following vaccination; N: number of evaluable participants.

*Antibody responses to serogroup A:*

At baseline, nearly all participants had SBA-BR titres ≥ 1:8; the differences among the groups in the proportions of baseline SBA-BR titres ≥ 1:8 and in baseline geometric mean titres (GMTs) were not statistically significant. At Day 28, all participants had SBA-BR titres ≥ 1:8. From Day 0 to Day 28, the SBA-BR GMTs (ranging from 3054 in the 1 µg group to

10865 in the 10 µg group) increased for each dosage group. The differences in Day 28 GMTs among the dosage groups were statistically significant ($p < 0.001$, analysis of variance [ANOVA]), even when taking into account the differences in the baseline titres ($p < 0.001$, analysis of covariance [ANCOVA]).

*Antibody responses to serogroup C:*

At baseline, the proportion of participants in each dosage group with SBA-BR titres ≥ 1:8 ranged from 35.7% in the 4 µg group to 42.3% in the 1 µg group. The differences were not statistically significant among the groups in the proportion of baseline SBA-BR titres ≥ 1:8 and in baseline GMT. From Day 0 to Day 28, the proportion of participants with SBA-BR titres ≥ 1:8 increased in each dosage group. In the 1 µg, 4 µg, and 10 µg dosage groups, Day 28 SBA-BR titres ≥ 1:8 were observed among 88.5%, 100.0%, and 100.0% of participants, respectively. The differences among the groups in the proportion of adults with Day 28 SBA-BR titres ≥ 1:8 were statistically significant ($p = 0.030$, Fisher's exact test), and represented a statistically significant trend ($p = 0.027$, Cochran-Armitage trend test). Likewise, the GMTs increased from Day 0 to Day 28 for each dosage group, where the Day 28 GMTs were higher in the 4 µg and 10 µg dosage groups (1559 and 1755, respectively) than in 1 µg recipients (540). The differences among the dosage groups in Day 28 GMT were statistically significant ($p = 0.041$, ANOVA), even when taking into account the differences in the baseline titres ($p = 0.022$, ANCOVA).

*Antibody responses to serogroup Y:*

At baseline, the proportions of participants with SBA-BR titres ≥ 1:8 in the 1 µg, 4 µg, and 10 µg dosage groups were 42.3%, 46.4%, and 63.0%, respectively. The baseline GMTs for the three dosage groups were 9.4, 19.0, and 28.1, respectively. The differences among the groups in the proportion of baseline SBA-BR titres ≥ 1:8 and in baseline GMT were not statistically significant. From Day 0 to Day 28, the proportion of participants with SBA-BR titres ≥ 1:8 increased for each dosage group to 84.6%, 89.3%, and 88.9%, respectively. The differences among the groups in the proportion of adults with Day 28 SBA-BR titres ≥ 1:8 were not statistically significant. The GMTs increased from Day 0 to Day 28 for each dosage group, with the Day 28 GMTs being higher in the 4 µg and 10 µg recipients (390 and 386, respectively) than in the 1 µg recipients (95). The differences among the groups in Day 28 GMT were not statistically significant, even when taking into account the differences in the baseline titre.

*Antibody responses to serogroup W-135:*

At baseline, the proportions of participants in the 1 µg, 4 µg, and 10 µg dosage groups with SBA-BR titres ≥ 1:8 were 30.8%, 53.6%, and 29.6%, respectively. The baseline GMTs for the three groups were 13.6, 10.0, and 9.8, respectively. The differences in the proportion of baseline SBA-BR titres ≥ 1:8 and in baseline GMT among the groups were not statistically significant. From Day 0 to Day 28, the proportion of participants with SBA-BR titres ≥ 1:8 increased to 88.5%, 85.7%, and 100.0%, respectively, for each dosage group. The differences among the groups in proportion of adults with Day 28 SBA-BR titres ≥ 1:8 were not statistically significant. The GMTs increased from Day 0 to Day 28 for each dosage group, and the Day 28 GMTs increased to 498, 608, and 1848, respectively, with increasing

Menactra vaccine dosage levels. The differences among the groups in Day 28 GMT were statistically significant (p = 0.041, ANOVA) and remained statistically significant (p = 0.022, ANCOVA) when considering the differences in the baseline titres.

For the four serogroups across the three dosage formulations, the results of the intent-to-treat (ITT) analysis were similar to those of the per-protocol (PP) analysis.

The 4 μg and 10 μg dose formulations had statistically higher immune responses in adults compared to the 1 μg dose formulation. The 4 μg and 10 μg dose formulations in adults also had higher rates of solicited local reactions compared to the 1 μg dose formulation. There were no differences in the rates of solicited systemic reactions as the dosage level was increased from 1 μg to 10 μg. The 4 μg formulation was selected for further clinical evaluation in children, adolescents, and adults based upon a balance between the safety and immunogenicity results obtained from these Phase I studies.

The three vaccine formulations were found to elicit comparable antibody responses to each of the four serogroups. The 4 μg dose formulation was selected for further evaluation based on the immune responses from this study.

## Efficacy

### Introduction

To establish the efficacy of Menactra vaccine, four different types of studies formed part of the development program. The first was comparatives (looking at efficacy and safety of Menactra versus the licensed polysaccharide Meningococcal vaccine Menomune); the second was a consistency study, examining the consistency of the immune response to three different lots of Menactra; the third was interference studies, looking at whether the co-administration of Menactra with other vaccines affected the immune response to either vaccine, and the fourth was two booster studies in children, examining the effect of prior vaccination with either a Meningococcal C vaccine or with Menactra followed by Menomune.

The three comparative clinical studies were designed to demonstrate that the immune response to Menactra vaccine is non-inferior to the immune response induced by the licensed polysaccharide Menomune vaccine. The comparative clinical studies were performed in children aged 2 to 10 years (Study 603-02), adolescents aged 11 to18 years (Study MTA02), and adults aged 18 to 55 years (Study MTA09). In these comparative clinical studies, non-inferiority between Menactra vaccine and Menomune vaccine was measured by the percentage of participants who had a ≥4-fold rise from baseline in SBA titre for each serogroup. The 4-fold rise in SBA titre was chosen as the primary serological endpoint for the following reasons:

- A 4-fold rise in SBA titre was the primary immunogenicity criterion for the licensure of the polysaccharide Menomune vaccine.

- A 4-fold rise in SBA titre is the WHO recommended method of evaluation for unconjugated meningococcal polysaccharide vaccines[19, 20].
- A 4-fold rise in SBA titre is considered a significant immunological response that correlates to efficacy[21], and should provide assurance that the clinical immune response to Menactra vaccine is non-inferior to the licensed comparator, Menomune vaccine.

In addition to the primary analysis of proportion of participants having 4-fold rise in SBA, other analyses were performed to support the evaluation of non-inferiority between Menactra vaccine and the licensed comparator vaccine. These included:

- Seroconversion rates, defined as the proportion of participants with a pre-vaccination SBA titre of < 1:8 and a post-vaccination titre ≥ 1:32;
- Geometric mean titres of the pre- and post-vaccination SBA titres; and
- Reverse cumulative distribution curves that graphically displayed the distribution of the pre- and post-vaccination SBA antibody titres.

In addition, antibodies were quantified for total IgG and IgM, in order to further compare and characterize the immune profile elicited by Menactra vaccine versus Menomune vaccine in a subset of participants aged 2 to 10 years and 11 to 17 years.

**Main Clinical Studies**

Dose response was investigated and established in Study 603-01(see above).

Immunogenicity data were available from nine studies. The data have been grouped based on the age of the subjects enrolled, study design and the primary objectives.

***Adults (Aged 18 to 55 years):***

*Study MTA09*

This study used the following methods to assess non-inferiority:

• the non-inferiority of the immune responses (defined as the upper two-sided 95% confidence limit of the percentage of participants presenting a ≥ 4-fold rise from baseline in serum bactericidal assay using baby rabbit complement [SBA-BR] titres in Menomune®-A/C/Y/W-135 recipients minus the corresponding percentage in Menactra vaccine recipients being less than 10%; and

• the non-inferiority of the safety profile (defined as the upper two-sided 95% confidence limit of the ratio of the percentage of participants presenting at least one severe solicited

[19]World Health Organization Expert Committee on Biological Standardization: Twenty seventh Report. WHO Tech Rep Ser. 1976;594:1-86

[20] World Health Organization Expert Committee on Biological Standardization: Thirty-first report. WHO Rep Ser. 1981:658:174-183

[21]Wong, KH, Barrera, O, Sutton, et al. Standardization and control of meningococcal vaccines, group A and group C polysaccharides. J Biol Stand. 1977;5:197-215

systemic reaction during the Day 0 to Day 7 period in the Menactra vaccine participants to the corresponding percentage in Menomune vaccine recipients being less than 3. This method is used to assess non-inferiority in all the comparative studies.

*Study MTA14*

This study conducted in the US was designed to demonstrate:

• the equivalence of the immune responses (defined as the upper two-sided 90% confidence limit of the ratio of post-vaccination adjusted geometric mean titre [GMT] of SBA-BR titres in participants who received three different lots of vaccine being less than 1.5 in Menactra vaccine recipients receiving three different consistency lots.

*Study MTA11*

This study conducted in the US was designed to demonstrate:

• the non-inferiority of the immune responses against the Salmonella typhi Vi antigen (defined as the upper two-sided 95% confidence limit of the percentage of participants developing anti-Vi antibody levels > 1 μg/mL in the Typhim Vi vaccine recipients minus the corresponding percentage in Menactra vaccine and Typhim Vi vaccine recipients being less than 10%); and

• the non-inferiority of the immune responses against meningococcal serogroups A, C, Y, and W-135.

***Adolescents (Aged 11 to 18 years):***

*Study MTA02*

This study conducted in the US was designed to demonstrate:

• the non-inferiority of the immune responses to Menactra vaccine versus Menomune vaccine recipients.

*Study MTA12*

This US study assessed the comparative safety and immunogenicity of the concomitant administration of Menactra and Td vaccine and was designed to demonstrate:

• the non-inferiority of the immune responses against the diphtheria and the tetanus antigens (defined as the upper two-sided 95% confidence limit of the percentage of participants developing an acceptable booster response for anti-diphtheria and anti-tetanus antibody levels in Td vaccine recipients minus the corresponding percentage in the Menactra and Td vaccine recipients being less than 10%); and

• the non-inferiority of the immune responses against meningococcal serogroups A, C, Y, and W-135 in Menactra vaccine recipients versus Menactra/Td vaccine recipients.

### *Children (Aged 2 to 10 years):*

*Study 603-02*
This study conducted in the US, assessed the comparative safety and immunogenicity study was designed to demonstrate:

• the non-inferiority of the immune responses to Menactra versus Menomune vaccine in recipients.

*Study MTA08*
This comparative safety study conducted in the US and Chile was designed to:

• document the safety profile of Menactra vaccine; and

• demonstrate the non-inferiority of the safety profile (defined as the upper two-sided 95% confidence limit of the ratio of the percentage of participants presenting at least one severe solicited systemic reaction during the Day 0 to Day 7 period in Menactra vaccine recipients to the corresponding percentage in the Menomune vaccine recipients being less than 3).

*Study MTA15*
This comparative immunogenicity study conducted in the UK was designed to demonstrate:

• the booster response to Menactra vaccine in participants who received a monovalent C meningococcal vaccine during infancy. The non-inferiority criteria for the booster response was based on the lower limit of the two-sided 95% CI of the percentage of participants presenting a ≥ 4-fold rise in SBA-BR serogroup C in Menactra vaccine recipients minus the corresponding percentage in the Hib conjugate vaccine[22] recipients being greater than 50%.

*Study MTA17 Stage I*
This comparative study of immune memory in the US designed to demonstrate:

• the immune memory responses by comparing the SBA-BR titres against the four meningococcal vaccine serogroups in subjects who had received one dose of Menactra

vaccine at least 18 months earlier in Study 603-02. Meningococcal vaccine-naïve, age-matched children were recruited as a control group. Each group received a reduced dose (1/10) of Menomune vaccine as a polysaccharide challenge.

### *Populations Evaluated*

The immunogenicity PP-participants are summarised as follows by age group:

• 3597 adults aged over 18 years;

• 1366 adolescents aged 11 to 18 years; and

• 753 children aged 2 to 10 years.

[22] A conjugate vaccine that provides immunization against infections caused by *Haemophilus influenzae* type b, especially bacterial meningitis and pneumonia in children.

### *Outcomes/endpoints*

*Measurement of SBA-BR – functional assay*

Immune responses to the antigens contained in the Menactra and Menomune vaccines were documented by the ability of the vaccines to induce serum antibodies in study participants displaying *in vitro* bactericidal activities to the four vaccine serogroups (A, C, Y, and W-135) of *N. meningitides* as described in the previous section. The following parameters were used to describe SBA-BR responses:

• Percentage of participants with a ≥ 4-fold rise in the SBA-BR titre with the corresponding confidence interval (CI) from Day 0 (baseline) to Day 28 (post-vaccination).

• Seroconversion rate with the corresponding CI. Seroconversion rate was defined as the number of participants who had a pre-vaccination SBA-BR titre < 1:8 at Day 0 and a postvaccination SBA-BR titre ≥ 1:32 (≥ 4-fold rise), divided by the total number of participants whose pre-vaccination SBA-BR titre was less than < 1:8 for each serogroup.

• Percentage of participants with SBA-BR titres ≥ 1:128 at Day 28.

• GMT with the corresponding CI at Day 0 and at Day 28.

• Geometric mean fold rise of SBA-BR titres with the corresponding CI from Day 0 to Day 28.

*Immunoglobulin G (IgG) and Immunoglobulin M (IgM) Responses*

In some studies, in addition to the assay to detect serum bactericidal antibodies, serum enzyme immunoassays (EIA) were performed to detect the presence of specific antibodies against the four serogroups of *N. meningitidis* (A, C, Y, and W-135).

• Geometric mean concentration (GMC) with corresponding CI at Day 0 and Day 28.

• Geometric mean fold-rise of titres with the corresponding CI from Day 0 to Day 28.

In addition, high avidity IgG antibodies against each of the four serogroups (A, C, Y, and W-135) were determined by a modified ELISA.

*Immune Responses to Other Antigens*

*Anti-Vi Responses*

In Study MTA11, immune responses to the Vi polysaccharide antigen contained in the Typhim Vi vaccine were measured by radioimmunoassay (RIA). Individual results were expressed as antibody concentrations (μg/mL).

The following parameters were used to describe anti-Vi responses:

• Percentage of participants with a post-vaccination antibody titre > 1.0 μg/mL.

• Percentage of participants with a ≥ 4-fold rise in antibody titre from Day 0 to Day 28.

• GMC on Day 0 and Day 28.

*Anti-diphtheria and Anti-tetanus Responses*

In Study MTA12, immune responses to the antigens contained in the Td vaccine were determined by EIA for tetanus toxoid and by micrometabolic inhibition test (MIT) using Vero cells for diphtheria toxoid. Individual results were expressed in antibody titres (IU/mL). The following parameters were used to describe anti-diphtheria and anti-tetanus responses:

• Booster response rate. The booster response rate was defined as the percentage of participants who presented a:

a) ≥ 4-fold increase in titre (from Day 0 to Day 28 post-Td vaccination) if the pre-vaccination titre (Day 0) was less than or equal to the cut-off value determined from historical data (1.28 IU/mL for diphtheria and 5.3 IU/mL for tetanus); or

b) ≥ 2-fold increase in titre (from Day 0 to Day 28 post-Td vaccination) if the pre-vaccination titre (Day 0) was higher than the cut-off value determined from historical data (1.28 IU/mL for diphtheria and 5.3 IU/mL for tetanus).

• Seroprotection rate (percentage of participants with a post-vaccination titre ≥ 1.0 IU/mL).

• Percentage of participants with a post-vaccination titre ≥ 0.1 IU/mL.

*Method and Timing of Measurements*

All pre-vaccination sera were collected prior to vaccine administration (Menactra vaccine, Menomune vaccine, placebo, Td vaccine, or Typhim Vi vaccine). All post-vaccination sera were collected 28 days after vaccine administration. In Study 603-02, to document the persistence of immune response, additional post-vaccination sera were collected six months after vaccine administration. Study MTA17 Stage I documented booster response in participants after they received a reduced dose (1/10) of Menomune vaccine; post-vaccination sera were collected 8 days or 28 days after vaccine administration.

*Statistical methods in Comparative studies of Menactra Vaccine and Menomune Vaccine*

The statistical objectives and hypotheses are summarised below for each study.

***Study MTA09 (Participants Aged 18 to 55 Years)***

*Primary (Immunogenicity) Objective and Hypothesis*

*Objective:* To compare response rates to each of the four meningococcal polysaccharide antigens (serogroups A, C, Y, and W-135) between treatment groups on Day 28 after vaccination with Menactra vaccine or Menomune vaccine (percentage of participants presenting a ≥ 4-fold rise from baseline in SBA-BR titres).

*Hypothesis*: The response rates of Menactra vaccine recipients should be non-inferior to the response rates of Menomune vaccine recipients. Non-inferiority was defined as the upper limit of the two-sided 95% CI of the difference in response rates being less than 10 percentage points.

The hypothesis was tested separately for each meningococcal antigen.

*Secondary (Immunogenicity) Objective and Hypothesis*

*Objective:* To compare the SBA-BR GMT for the four meningococcal polysaccharide antigens (serogroups A, C, Y, and W-135) on Day 28 after administration of Menactra vaccine or Menomune vaccine. To avoid the effect of any imbalanced baseline titres, adjusted GMT ($log^2$ Day 28 titre minus $log^2$ baseline titre) was calculated and modeled using $log^2$ baseline as a covariate in the analysis of covariance.

*Hypothesis*: The Day 28 post-vaccination adjusted GMT of Menactra vaccine recipients should be non-inferior to the post-vaccination, adjusted GMT of Menomune vaccine recipients. Non-inferiority was defined as the upper limit of the two-sided 95% CI of the ratio of the GMTs being less than 2. The hypothesis was tested separately for each meningococcal antigen.

***Study MTA02 (Participants Aged 11 to 18 Years)***

*Primary Objective and Hypothesis*: as for **Study MTA09.** Upper limit of the two-sided 95% CI of the difference in response rates was also used. No secondary (immunogenicity) objective was defined in this study.

***Study 603-02 (Participants Aged 2 to 10 Years)***

*Primary Objective and Hypothesis*: as for **Study MTA09.** No secondary immunogenicity objective was defined in this study.

***Lot Consistency Study MTA14 (Participants Aged 18 to 55 Years)***

*Primary (Immunogenicity) Objective and Hypothesis*

Objective: To compare the SBA-BR GMT for each of the four polysaccharide antigens (serogroups A, C, Y, and W-135) 28 days after vaccination with Menactra vaccine (three consecutive lots designated Lot 1, Lot 2, and Lot 3). To avoid the effect of any imbalanced baseline titres, adjusted GMT ($log^2$ Day 28 titre minus $log^2$ baseline titre) was calculated and modeled using $log^2$ baseline as a covariate in the analysis of covariance.

*Hypothesis*: The Day 28 post-vaccination, adjusted GMT for participants in any of the three Menactra vaccine consistency-lot groups (Menactra vaccine Lot 1, Lot 2, and Lot 3) should be equivalent. Equivalence was defined as the upper limit of the two-sided 90% CI of the ratio (of the most immunogenic lots adjusted GMT divided by the least immunogenic lots adjusted GMT) being less than 1.5. The hypothesis was tested separately for each meningococcal antigen.

*Secondary (Immunogenicity) Objective and Hypothesis*

Objective: To compare response rates (percentage of participants developing a ≥ 4-fold rise in their SBA-BR titre, from Day 0 (baseline) to Day 28 (post-vaccination) to each of the four polysaccharide antigens (A, C, Y, and W-135) in each of the three consistency-lot groups (Menactra vaccine Lot 1, Lot 2, and Lot 3) 28 days after vaccination.

*Hypothesis*: The response rates of participants in any two of the three consistency-lot groups (Menactra vaccine Lot 1, Lot 2, and Lot 3) should be equivalent. The hypothesis was tested separately for each meningococcal antigen.

### *Interference Studies*

#### *Study MTA12 (Participants Aged 11 to 17 Years)*

Two co-primary objectives were defined. The general objectives were to demonstrate that Menactra vaccine does not negatively interfere with the immune responses induced by the Td vaccine, and conversely, that the Td vaccine does not negatively interfere with the immune responses elicited by Menactra vaccine.

*Primary (Immunogenicity) Objectives and Hypotheses*

1) To compare the booster response rate to diphtheria and tetanus antigens between treatment groups 28 days post-Td vaccination.

*Hypothesis*: The booster response rate of Group A participants (defined above) should be non-inferior to the booster response rate of Group B participants (defined above).

The hypothesis was tested separately for the diphtheria and tetanus antigens.

2) To compare the response rates to each of the four meningococcal polysaccharide antigens (serogroups A, C, Y, and W-135) between treatment groups on Day 28 after Menactra vaccination (percentage of participants developing a ≥ 4-fold rise from baseline in SBA-BR titres).

*Hypothesis*: The Day 28 post-Menactra vaccination response rate of Group A participants should be non-inferior to the Day 28 post-Menactra vaccination response rate of Group B participants. The hypothesis was tested separately for each of the four meningococcal antigens.

*Secondary (Immunogenicity) Objectives and Hypotheses*

1) To compare response rates to diphtheria and tetanus on Day 28 after Td vaccination between treatment groups (percentage of participants developing anti-diphtheria and anti-tetanus titres ≥ 1.0 IU/mL).

*Hypothesis*: The response rate of Group A participants should be non-inferior to the seroprotection rate of Group B participants.

The hypothesis was tested separately for the diphtheria and tetanus antigens.

2) To compare anti-diphtheria and anti-tetanus GMTs between treatment groups on Day 28 post-Td vaccination.

*Hypothesis*: The Day 28 post-Td vaccination GMTs of Group A participants should be non inferior to the Day 28 post-Td-vaccination GMTs of Group B participants. Non-inferiority was defined as the upper limit of the two-sided 95% CI of the ratio of the GMTs being less than 2. The hypothesis was tested separately for the diphtheria and tetanus antigens.

3) To compare SBA-BR GMTs between treatment groups on Day 28 post-Menactra vaccination.

*Hypothesis*: The Day 28 post-Menactra-vaccination GMTs of Group A participants should be non-inferior to the Day 28 post-Menactra-vaccination GMTs of Group B participants. Non-

inferiority was defined as the upper limit of the two-sided 95% CI of the ratio of the GMTs being less than 2. The hypothesis was tested separately for each of the four meningococcal antigens.

An observational immunogenicity objective with two corresponding hypotheses was defined.

*Observational (Immunogenicity) Objective and Hypothesis*

*Objective*: No impact should be observed as a result of the concomitant administration of Td vaccine or prior use of Td vaccine (28 days) on the ability to respond to Menactra antigens. For each of the two study groups (Group A and Group B), a comparison to a historically relevant data set (Study MTA02; SBA-BR GMT post-Menactra vaccination data) was performed.

*Hypothesis:* The Day 28 post-Menactra vaccination GMTs of Group A participants (those who received Td and Menactra vaccines concomitantly, followed by placebo 28 days later) and Group B participants (those who received Td vaccine and placebo concomitantly, followed by Menactra vaccine 28 days later) should be non-inferior to the GMTs of participants belonging to the MTA02 study relevant data set. Non-inferiority was defined as the upper limit of the two sided 95% CI of the ratio of the GMTs being less than 2. Two sets of hypothesis testing (Group A and Group B) were performed for each of the four meningococcal antigens.

***Study MTA11 (Participants Aged 18 to 55 Years)***

Two co-primary objectives were defined. The general objectives were to demonstrate that Menactra vaccine did not negatively interfere with the immune responses induced by the typhoid vaccine, and conversely, that the typhoid vaccine did not negatively interfere with the immune responses elicited by Menactra vaccine.

*Primary (Immunogenicity) Objectives and Hypotheses*

1) To compare response rates to the Typhim Vi vaccine antigen 28 days post-typhoid vaccination between treatment groups (percentage of participants developing anti-Vi antibody levels > 1 μg/mL).

*Hypothesis*: The response rate of Group A participants (those who received Typhim Vi vaccine and Menactra vaccine concomitantly, followed by placebo 28 days later) should be non-inferior to the response rate of Group B participants (those who received Typhim Vi vaccine and placebo concomitantly, followed by Menactra vaccine 28 days later).

2) To compare the response rates to each of the four meningococcal polysaccharide antigens (serogroups A, C, Y, and W-135) between treatment groups on Day 28 after administration of Menactra vaccine (percentage of participants developing a ≥ 4-fold rise from baseline in SBA-BR titres).

*Hypothesis*: The Day 28 post-Menactra vaccine response rate of Group A participants (those who received Typhim Vi vaccine and Menactra vaccines concomitantly, followed by placebo 28 days later) should be non-inferior to the Day 28 post-Menactra vaccination response rate

of Group B participants (those who received Typhim Vi vaccine and placebo concomitantly, followed by Menactra vaccine 28 days later). The hypothesis was tested separately for each of the four meningococcal antigens.

In addition, secondary objectives and corresponding hypotheses were defined.

*Secondary (Immunogenicity) Objectives and Hypotheses*
1) To compare anti-Vi GMT on Day 28 post-vaccination with Typhim Vi vaccine between treatment groups.

*Hypothesis*: The post-typhoid vaccination anti-Vi GMT of Group A participants (those who received Typhim Vi vaccine and Menactra vaccine concomitantly, followed by placebo 28 days later) should be non-inferior to the post-typhoid vaccination anti-Vi GMT of Group B participants (those who received Typhim Vi vaccine and placebo concomitantly, followed by Menactra vaccine 28 days later). Non-inferiority was defined as the upper limit of the two-sided 95% CI of the ratio of the GMTs being less than 2.

2) To compare SBA-BR GMTs on Day 28 post-Menactra vaccination between treatment groups.

*Hypothesis*: The Day 28 post-Menactra vaccine adjusted GMT of Group A participants (those who received Typhim Vi and Menactra vaccines concomitantly, followed by placebo 28 days later) should be non-inferior to the Day 28 post- Menactra vaccination adjusted GMT of Group B participants (those who received Typhim Vi vaccine and placebo concomitantly, followed by Menactra vaccine 28 days later). Non-inferiority was defined as the upper limit of the two-sided 95% CI of the ratio of the GMTs being less than 2. To avoid the effect of any imbalanced baseline titres, adjusted GMT ($log^2$ Day 28 titre minus $log^2$ baseline titre) was calculated and modeled using $log^2$ baseline as a covariate in the analysis of covariance.

The hypothesis was tested separately for each of the four meningococcal antigens.

### *Booster studies*

### *Study MTA17 Stage I*

Study MTA17 Stage I, a comparative study conducted in the US was designed to document the immune responses in a subset of participants who were primed with Menactra vaccine two years earlier in Study 603-02. No statistical hypotheses were tested.

### *Study MTA15*

This was a randomized comparative study conducted in the UK was designed to demonstrate the ability of Menactra vaccine to boost the serogroup C antibody responses in children primed in infancy with a monovalent meningococcal C conjugate vaccine. Participants were randomized to receive either Menactra vaccine or a Hib control vaccine. Menactra vaccine was considered superior to the control group antibody responses if the difference between the proportion of participants who have ≥ 4-fold rise in serogroup C titres in the group receiving Menactra vaccine and the proportion of participants who have ≥ 4-fold rise in serogroup C titres in the group receiving a licensed Hib conjugate vaccine was > 50%. Immunogenicity parameters included serum SBA-BR antibody titres and serum IgG concentrations for serogroups A, C, Y, and W-135.

### *Safety Study MTA08 in children with an immunogenicity subset as an observational objective*

Study MTA08, a randomized, modified double-blind, active-controlled, multicenter study conducted in the US and Chile was designed to:

• document the safety profile of Menactra vaccine; and

• demonstrate the non-inferiority of the safety profile (defined as the upper limit of the two-sided 95% CI of the ratio of the percentage of participants presenting at least one severe solicited systemic reaction during the Day 0 to Day 7 period in Menactra vaccine recipients to the corresponding percentage in the Menomune vaccine recipients being less than 3). Two of the observational objectives were to document the (Day 28) immune responses against meningococcal serogroups A, C, Y, and W-135 in a subset of Menactra vaccine and Menomune vaccine in Chilean recipients. Immunogenicity parameters included serum SBA-BR antibody titres and serum IgG concentrations for serogroups A, C, Y, and W-135.

### *Definitions of Per-Protocol Populations*

For the studies considered in this section, the PP populations were defined as including all study participants meeting the following criteria:

1) Received the assigned vaccine;

2) Underwent blood sampling on Day 0;

3) Underwent subsequent blood sampling as specified in the study protocol. Participants without any valid serology results were excluded from the PP population analysis. The PP population included some participants who had protocol violations, which were judged to have low or no probability of affecting their immunologic response, such as a participant who did not record his/her temperature for one day during the 7-day diary period or for whom the site was unable to collect a full protocol-specified amount of blood at a scheduled visit. This decision was made on an individual basis by a blinded medical monitor, before unblinding the treatment assignment

### *Studies in Adults*

### *Study MTA09*

Study MTA09 was a randomized, modified double-blind, active-controlled, multicenter comparative safety and immunogenicity study conducted in the US. Following vaccination, blood specimens (approximately 10 mL whole blood) for serologic testing were drawn on Day 0 prior to vaccination (baseline) and on Day 28 after vaccination. At each of these time points, sera were assayed for anti-meningococcal antibodies to serogroups A, C, Y, and W-135.

The study included more females than males (61.1% and 63.1% compared to 38.9% and 36.9%in the Menactra and Menomune groups, respectively) and the mean and median ages of the participants were 29-29.1 years and 24 years (in both groups), respectively (the range was 18-55 in both groups). The majority of subjects were Caucasian (84.8-85.3%)

with similar numbers of Black and Hispanic participants (5.1-5.9%). A smaller number of Asian (2.6-2.9%) and Other (1.1-1.6%) were also included.

The baseline distributions of participants by sex, age, and race were not statistically different between the two treatment groups (p-values were 0.307, 0.765, and 0.842, respectively). The results of immunogenicity Day 0 and Day 28 are presented in Table 6.

**Table 6: Study MTA09, Descriptive Immunogenicity Results: SBA-BR Antibody Titer (Per-protocol Population)**

| | | Menactra Vaccine | | Menomune Vaccine | |
|---|---|---|---|---|---|
| **Immune Response Parameter** | **Serogroup** | **$N_T$*** | **% or Titer** | **$N_M$*** | **% or Titer** |
| **Percentage of participants with ≥ 4-fold rise** | A | 1280 | 80.5 | 1098 | 84.6 |
| | C | 1280 | 88.5 | 1098 | 89.7 |
| | Y | 1280 | 73.5 | 1098 | 79.4 |
| | W-135 | 1280 | 89.4 | 1098 | 94.4 |
| **Geometric mean titer on Day 0** | A | 1280 | 223.8 | 1098 | 203.6 |
| | C | 1280 | 56.8 | 1098 | 51.7 |
| | Y | 1280 | 123.2 | 1098 | 127.2 |
| | W-135 | 1280 | 33.1 | 1098 | 30.9 |
| **Geometric mean titer on Day 28** | A | 1280 | 3896.9 | 1098 | 4114.1 |
| | C | 1280 | 3231.1 | 1098 | 3469.4 |
| | Y | 1280 | 1750.4 | 1098 | 2448.6 |
| | W-135 | 1280 | 1271.0 | 1098 | 1871.2 |
| **Geometric mean fold-rise in antibody titers** | A | 1280 | 16.0 | 1098 | 18.5 |
| | C | 1280 | 47.2 | 1098 | 55.4 |
| | Y | 1280 | 12.2 | 1098 | 16.7 |
| | W-135 | 1280 | 31.4 | 1098 | 49.2 |
| **Percentage of participants seroconverting (Day 0 titer < 1:8 and Day 28 titer ≥ 1:32)** | A | 156 | 100.0 | 144 | 99.3 |
| | C | 345 | 99.4 | 304 | 97.7 |
| | Y | 279 | 90.7 | 228 | 96.9 |
| | W-135 | 373 | 96.5 | 328 | 99.1 |
| **Percentage of participants with Day 28 titer ≥ 1:128** | A | 1280 | 99.8 | 1098 | 99.9 |
| | C | 1280 | 98.8 | 1098 | 98.5 |
| | Y | 1280 | 97.0 | 1098 | 98.5 |
| | W-135 | 1280 | 97.1 | 1098 | 98.5 |

$N_T$ and $N_M$ represent the total number of participants for whom the immune response criterion was calculated (who had valid serology data) in the Menactra vaccine and Menomune vaccine groups, respectively.

*Assessment of Study Primary Hypothesis 2:*

The study hypothesis was that the Menactra vaccine was non-inferior to Menomune vaccine 28 days post-vaccination. This was assessed the proportion of participants with a ≥ 4-fold rise from baseline in the SBA-BR titres for *N. meningitidis* serogroups A, C, Y, and W-135.

To demonstrate the non-inferiority of Menactra vaccine versus Menomune vaccine, the following criterion was to hold simultaneously for the four serogroups at Day 28:

- For serogroups A, C, Y, and W-135, the upper limit of the two-sided 95% CI of *p Menomune* - *p Menactra* < 0.10, where *p* represented the proportion with a ≥ 4-fold rise in SBA-BR titre from baseline.

In the Menactra vaccine group, the percentages for the serogroups A (80.5%), C (88.5%), Y (73.5%), and W-135 (89.4%) were comparable to those in the Menomune group (84.6%, 89.7%, 79.4%, and 94.4% for serogroups A, C, Y, and W-135, respectively). The upper limits of the two-sided 95% CIs of the differences between the proportions for Menomune minus the corresponding proportions for Menactra were 7.18%, 3.70%, 9.30%, and 7.15% for serogroups A, C, Y, and W-135, respectively, which was below the non-inferiority margin of 10%.

Based on these results, the primary immunogenicity null hypothesis was rejected; therefore Menactra vaccine was considered non-inferior to Menomune vaccine using a 10% non-inferiority margin and Type 1 error rate of α = 0.025.

*Assessment of Study Secondary Hypothesis:*

The hypothesis tested that 28 days post-vaccination, the SBA-BR GMT of each of the serogroups A, C, Y, and W-135 in the Menactra vaccine group was non-inferior to the GMT of the same serogroup in the Menomune vaccine group. To evaluate the secondary hypothesis, the difference of the $\log^2$ of the post- and pre-vaccination titres of SBA-BR for *N. meningitidis* serogroups A, C, Y, and W-135 was calculated. A linear regression model was fitted using this difference as a dependent variable, and the treatment group and the $\log^2$ pre-vaccination titre as independent variables, using PROC MIXED in SAS®[23] . A two-sided 95% CI was calculated for the difference between the estimated effect in the Menomune vaccine group (τM*enomune*) minus the corresponding effect in the Menactra vaccine group (τ*Menactra*). To demonstrate the non-inferiority of Menactra vaccine to Menomune vaccine, the following criterion had to hold simultaneously for the four serogroups on Day 28: For serogroups A, C, Y, and W-135, the upper limit of the two-sided 95% CI of τ*Menomune* - τ*Menactra* < $\log^2$, where τ*Menomune* and τ*Menactra* were the estimated effects in the groups receiving Menomune vaccine and Menactra vaccine, respectively. The upper limits of the two-sided 95% CIs of the ratios were 1.17, 1.24, 1.56 and 1.67 for serogroups A, C, Y, and W-135, respectively, which was below the non-inferiority margin of 2.

Based on these results, the secondary null hypothesis (H0: GMT Menomune vaccine / GMT Menactra vaccine ≥ 2) was rejected, and the non-inferiority of Menactra vaccine was concluded using 2 as a non-inferiority margin and Type 1 error rate of α = 0.025.

### *Study MTA14*

A total of 1582 participants constituted the immunogenicity population in the lot consistency comparison of this trial. They were divided evenly among the three Menactra vaccine lots. A total of 458 participants constituted the safety population in the Menomune vaccine arm for the safety comparison of this trial.

[23] PROC MIXED SAS provides accessibility to numerous mixed linear models that are used in many common statistical analyses.

The study included more females than males (62.5-63.8% compared to 36.2-37.5% across the groups, respectively) and the mean and median ages of the participants were 28.9-29.1 years and 24 years, respectively (the range was 18-55 in all groups). The majority of subjects were Caucasian (85.4-86.6%) with smaller numbers of Black (5.7-6.8%) and Hispanic participants (3.8-5.9%). A smaller number of Asian (1.1-3.0%) and Other (0.8-1.3%) were also included. The demographic characteristics (sex, age, and race) were not statistically significantly different between the groups. The age categories were also not statistically significantly different for subjects who received Menactra vaccine Lots 1, 2, and 3. The results of immunogenicity on Day 0 and Day 28 are presented in Table 7.

**Table 7: Study MTA14, Descriptive Immunogenicity Results: SBA-BR Antibody Titer (Per-protocol population)**

| | | Menactra Vaccine Lot 1 | | Menactra Vaccine Lot 2 | | Menactra Vaccine Lot 3 | |
|---|---|---|---|---|---|---|---|
| Immune Response Parameter | Serogroup | $N_1$* | % or Titer | $N_2$* | % or Titer | $N_3$* | % or Titer |
| Percentage of participants with ≥ 4-fold rise | A | 495 | 85.1 | 486 | 85.4 | 499 | 81.6 |
| | C | 495 | 85.9 | 486 | 89.5 | 499 | 83.2 |
| | Y | 495 | 74.9 | 486 | 71.6 | 499 | 80.6 |
| | W-135 | 495 | 86.1 | 486 | 88.1 | 499 | 91.8 |
| Geometric mean titer on Day 0 | A | 496 | 239.1 | 486 | 271.4 | 499 | 248.6 |
| | C | 496 | 72.6 | 486 | 57.3 | 499 | 79.3 |
| | Y | 496 | 243.8 | 486 | 184.7 | 499 | 208.4 |
| | W-135 | 496 | 47.4 | 486 | 48.5 | 499 | 44.5 |
| Geometric mean titer on Day 28 | A | 495 | 8169.1 | 486 | 8215.4 | 499 | 6679.0 |
| | C | 495 | 3867.5 | 486 | 4154.8 | 499 | 3216.6 |
| | Y | 495 | 2898.3 | 486 | 2472.2 | 499 | 3805.3 |
| | W-135 | 495 | 2030.9 | 486 | 2573.0 | 499 | 2456.7. |
| Geometric mean fold-rise in antibody titers | A | 495 | 30.0 | 486 | 26.7 | 499 | 23.4 |
| | C | 495 | 44.0 | 486 | 59.0 | 499 | 33.8 |
| | Y | 495 | 10.7 | 486 | 11.9 | 499 | 16.2 |
| | W-135 | 495 | 33.4 | 486 | 41.8 | 499 | 43.7 |
| Percentage of participants seroconverting (Day 0 titer < 1:8 and Day 28 titer ≥ 1:32) | A | 94 | 100.0 | 87 | 100.0 | 99 | 100.0 |
| | C | 139 | 95.7 | 144 | 100.0 | 131 | 96.9 |
| | Y | 73 | 95.9 | 85 | 92.9 | 88 | 96.6 |
| | W-135 | 176 | 94.9 | 167 | 94.6 | 169 | 97.6 |
| Percentage of participants with Day 28 titer ≥ 1:128 | A | 495 | 100.0 | 486 | 100.0 | 499 | 99.8 |
| | C | 495 | 97.4 | 486 | 99.0 | 499 | 96.6 |
| | Y | 495 | 99.2 | 486 | 97.9 | 499 | 98.4 |
| | W-135 | 495 | 96.8 | 486 | 96.3 | 499 | 98.2 |

*Assessment of Study Primary Hypothesis:*

The hypothesis tested that 28 days after vaccination, the immune responses to the three consistency lots of Menactra vaccine, as measured by the geometric mean titre (GMT), was equivalent for each of the four serogroups. The differences in treatment effect (maximum-minimum) were, in order of magnitude, 0.297 (serogroup A), 0.334 (serogroup W-135), 0.459 (serogroup C), and 0.579 (serogroup Y). To test this primary hypothesis, the two-sided 90% CI of the treatment effect difference (maximum-minimum) was determined, and the result was converted by taking the antilog[2]. The immune responses to the three consistency lots of Menactra vaccine were considered equivalent if the upper limit of the two-sided 90% CI of the treatment effect difference was < log[2] (1.5). This criterion was met for the immune response to serogroup A (1.390) and serogroup W-135 (1.491), but not for serogroup C (1.637) or serogroup Y (1.734). Similar results were obtained with the intent-to-treat population, with the equivalence criteria being met for the immune response to

serogroup A (1.402) and serogroup W-135 (1.479), but not for serogroup C (1.626) or serogroup Y (1.757).

*Assessment of Study Secondary Hypothesis 2:*
The three Menactra vaccine lots were considered to be consistent if the upper limit of the two sided 95% CI of the difference *p*max - *p*min was < 0.1, where *p*max and *p*min were the maximum and the minimum proportions among the three lot responses. The differences due to treatment *p*max - *p*min were, in order of magnitude, 3.8% (serogroup A), 5.7% (serogroup W-135), 6.3% (serogroup C), and 9.0% (serogroup Y. To test this Secondary Hypothesis 2, the two-sided 95% CI of the treatment effect difference (*p*max - *p*min ) was determined, and converted to percentage. The immune responses to the three lots of Menactra vaccine were considered equivalent if the upper limit of the two-sided 95% CI of the treatment effect difference was < 10%. This criterion was met for the immune response to serogroup A (8.5%) and serogroup W-135 (9.6%), but not for serogroup C (10.6%) or serogroup Y (14.3%). Similar results were obtained with the ITT population, with the criteria being met for the immune response to serogroup A (8.4%) and serogroup W-135 (9.3%), but not for serogroup C (10.5%) or serogroup Y (14.3%). A reverse cumulative distribution curve was constructed for each serogroup in three lots of vaccine These figures showed consistency in the responses for all serogroups among the three lots in the range of antibody responses considered to be protective. At higher levels of antibody response (> 4096), there was some divergence in consistency seen for the Y and C serogroups.

Although the statistical criteria for serogroup C and Y were not met, this was at responses beyond those considered protective and is unlikely to have clinical significance.

***Study MTA11***

Participants were randomized to one of two treatment groups. There were a total of three visits, two vaccination visits followed by a final third visit when blood was collected. Participants in Group A and Group B received two consecutive vaccinations on Day 0 and one vaccination on Day 28. The vaccination schedules of Group A and Group B were:

- ***Group A***: Typhim Vi vaccine and Menactra vaccine on Day 0 (Visit 1) and placebo on Day 28 (Visit 2).
- ***Group B***: Typhim Vi vaccine and placebo on Day 0 (Visit 1) and Menactra vaccine on Day 28 (Visit 2).

The age range for this trial was from 18 to 55 years of age. Blood was collected from all participants before vaccinations, 28 days after vaccinations and at each visit for the assessment of antibody levels to the trial vaccines.

The study included more females than males (67.2-69.1% compared to 30.9-32.8%, respectively), the mean and median ages of the participants were 32.5-32.8 years and 30.0-31.0 years, respectively (the range was 18-55 in both groups). The majority of subjects were Caucasian (71.9-74.6%) with smaller numbers of Black (9.9-11.3%) and Hispanic participants (11.3-11.6%). A smaller number of Asian (2.3-3.8%) and Other (1.7%) were also included. The baseline distributions of participants by sex, age, and race were not

statistically different between the two treatment groups (p-values: 0.577, 0.663, and 0.648, respectively). Table 8 describe the results of immunogenicity of the two vaccines administered during that study on Day 0 and Day 28 (Day 0 and Day 28 refers to the time elapsed from the time of administration of Menactra vaccine or Typhim Vi vaccine).

**Table 8: Study MTA11: Descriptive Immunogenicity Results: SBA-BR Antibody Titer (Per-protocol Population)**

| | | Group A* | | Group B† | |
|---|---|---|---|---|---|
| **Immune Response Parameter** | **Serogroup** | **N‡** | **% or Titer** | **N*** | **% or Titer** |
| **Percentage of participants with ≥ 4-fold rise** | A | 418 | 79.67 | 419 | 75.18 |
| | C | 418 | 89.47 | 419 | 88.31 |
| | Y | 418 | 74.40 | 419 | 65.16 |
| | W-135 | 418 | 85.17 | 419 | 83.77 |
| **Geometric mean titer on Day 28** | A | 419 | 5137.92 | 420 | 5109.79 |
| | C | 419 | 3061.35 | 420 | 3145.44 |
| | Y | 419 | 1821.04 | 420 | 1742.17 |
| | W-135 | 419 | 1002.21 | 420 | 928.99 |

Group A: Typhim Vi vaccine + Menactra vaccine, then placebo. Group B: Typhim Vi vaccine + placebo, then Menactra vaccine. N represents the total number of participants for whom the immune response criterion was calculated (i.e., who had valid serology data) in each group.

*Assessment of Study Primary Hypothesis 1:*

The hypothesis tested that 28 days post-vaccination with Typhim Vi vaccine, the proportion of participants achieving a protective level of antibody to the Vi antigen when given concomitantly with Menactra vaccine was non-inferior to the proportion of participants who achieved protective levels of antibody to the Vi antigen when given with placebo. The proportion of participants with Vi antibody titre > 1.0 µg/mL on Day 28 following Typhim Vi vaccination was higher in Group A than in Group B participants (the difference between the proportion in Group B and the proportion in Group A was - 3.11%). The upper limit of the two-sided 95% CI of the difference was 2.31%. This limit was below the non-inferiority margin of 10% (or 0.1). So non-inferiority could be concluded using 10% as a non-inferiority margin and Type 1 error rate of $\alpha = 0.025$.

*Assessment of Study Primary Hypothesis 2:*

Table 8 shows the numbers and proportions of participants with a ≥ 4-fold rise in SBA-BR antibody titre from baseline to Day 28 following the Menactra vaccination for serogroups A, C, Y, and W-135. For each serogroup, these proportions were higher in Group A than in Group B participants (the differences between the proportions in Group B and in Group A participants were - 4.49%, - 1.17%, - 9.25%, and - 1.40% for serogroups A, C, Y, and W-135, respectively). The upper limits of the two-sided 95% CIs of the differences were 1.17%, 3.09%, - 3.06%, and 3.51% for serogroups A, C, Y, and W-135, respectively. These limits were below the non-inferiority margin of 10% (or 0.1). Based on these results, non-inferiority was concluded using 10% as a non-inferiority margin and Type 1 error rate of $\alpha=0.025$.

*Assessment of Study Secondary Hypothesis 1:*

This non-inferiority hypothesis was defined by the upper limit of the two-sided 95% CI of the ratio of GMT Vi + placebo / GMT Vi + Menactra < 2, where GMT Vi + placebo and GMT Vi + Menactra were the anti-Vi GMT from the Typhim Vi vaccine + placebo group participants (Group B) and the anti-Vi GMT from the Typhim Vi vaccine + Menactra vaccine group participants (Group A), respectively. The anti-Vi GMT was higher in Group A than in Group B participants (the ratio of the GMT in Group B to the GMT in Group A was 0.86). The upper limit of the two-sided 95% CI of the GMT ratio was 1.0. This limit was below the non-inferiority margin of 2. So again, non-inferiority was concluded using 2 as a non-inferiority margin and Type 1 error rate of $\alpha = 0.025$.

*Assessment of Study Secondary Hypothesis 2:*

The non-inferiority hypothesis was defined by the upper limit of the two sided 95% CI of GMT Menactra / GMT Vi + Menactra < 2, where GMT Menactra and GMT Vi + Menactra were the GMTs from the participants receiving Typhim Vi vaccine + placebo followed by Menactra vaccine 28 days later (Group B) and the participants receiving Typhim Vi vaccine + Menactra vaccine concomitantly (Group A), respectively. GMTs were calculated as the $\log^2$ titre at Day 28 following the Menactra vaccination adjusted for baseline disparities in the pre-existing antibody analysis of covariance with the baseline outcome as a covariate. For each serogroup, the estimated treatment effects were higher in Group A than in Group B (the differences between the estimated $\log^2$ of the effects in Group B and the ones in Group A were - 0.129, - 0.082, - 0.265, and - 0.147 for serogroups A, C, Y, and W-135, respectively). The differences between the $\log^2$ of the vaccine effects were estimated by modeling the calculated difference of the $\log^2$ of the post- and pre-vaccination titres of SBA-BR for *N. meningitidis* serogroups A, C, Y, and W-135 as a dependent variable and using the treatment group and the $\log^2$ pre-vaccination titre as independent variables. The upper limits of the two sided 95% CIs of the differences of $\log^2$ of the effects were 0.13, 0.28, 0.07, and 0.25 for serogroups A, C, Y, and W-135, respectively. These limits were well below the non-inferiority margin of $\log^2$ (2) (or 1). Based on these results, non-inferiority was concluded using 2 as a non-inferiority margin and Type 1 error rate of $\alpha = 0.025$.

Both primary objectives were met for this study supporting the conclusion that Menactra vaccine can be concomitantly administered with Typhim Vi vaccine.

### *Studies in Adolescents*

### *Study MTA02*

Eligible participants for whom informed consent had been granted were randomized to receive a single injection of either Menactra vaccine or Menomune vaccine. No concomitant vaccines were administered with the trial products. Blood specimens (at least 5 mL whole blood) for serologic testing were drawn on Day 0 prior to vaccination (baseline) and at Day 28 post-vaccination (to assess primary immune response). At each of these time points, sera were assayed for bactericidal antibodies to meningococcal serogroups A, C, Y, and W-135. Additionally, a subset of participants was also tested for IgG and IgM antibodies.

The study included slightly more males than females (53.6-56.7% compared to 43.3-46.4%, respectively), the mean and median ages of the participants were 14.3 years and 14.0 years, respectively (the range was 11-18 in both groups). The majority of subjects were Caucasian (94.8-95.73%) with similar numbers of Black (3.2-3.4%) and Hispanic participants (0.2-0.5%). A smaller number of Asian (0.2%) and Other (0.7-1.1%) were also included.

The baseline distributions of participants by sex, age, and race were not statistically different between the two treatment. Tables 9-11 describe the results of immunogenicity on Day 0 and Day 28 for SBA-BR, IgG, and IgM titres, respectively.

*Assessment of Study Primary Hypothesis:*

The hypothesis tested that at 28 days after vaccination, Menactra vaccine was non-inferior to Menomune vaccine by the proportion of participants with a ≥ 4-fold rise in SBA-BR titres for *N. meningitidis* serogroups A, C, Y, and W-135. To demonstrate the non-inferiority of Menactra vaccine to Menomune vaccine, the following criteria must hold true simultaneously for the four serogroups at Day 28: For serogroups A, C, Y, and W-135, the upper limit of the one-sided 95% CI of *p* Menomune - *p* Menactra < 0.10 where *p* represented the proportion of participants with a SBA-BR titre ≥ 4-fold rise from baseline. For each serogroup, these percentages were higher in the Menactra vaccine group than in the Menomune vaccine group. The upper limits of the one-sided 95% CIs of the differences between these proportions were 2.73%, 0.29%, 2.78%, and 0.80% for serogroups A, C, Y, and W-135, respectively, which was below the non-inferiority margin of 10%. Based on these results, non-inferiority was concluded using a non-inferiority margin of 10% and Type 1 error rate of $\alpha = 0.05$.

**Table 9: Study MTA02, Descriptive Immunogenicity Results: SBA-BR Titers (Per-protocol Population)**

| | | Menactra Vaccine | | Menomune Vaccine | |
|---|---|---|---|---|---|
| **Immune Response Parameter** | **Serogroup** | **$N_T$*** | **% or Titer** | **$N_M$*** | **% or Titer** |
| **Percentage of participants with ≥ 4-fold rise** | A | 423 | 92.7 | 423 | 92.4 |
| | C | 423 | 91.7 | 423 | 88.7 |
| | Y | 423 | 81.8 | 423 | 80.1 |
| | W-135 | 423 | 96.7 | 423 | 95.3 |
| **Geometric mean titer on Day 0** | A | 425 | 106.28 | 423 | 88.67 |
| | C | 425 | 33.71 | 423 | 37.39 |
| | Y | 425 | 103.21 | 423 | 111.91 |
| | W-135 | 425 | 20.70 | 423 | 23.90 |
| **Geometric mean titer on Day 28** | A | 423 | 5483.21 | 423 | 3245.67 |
| | C | 423 | 1924.36 | 423 | 1638.87 |
| | Y | 423 | 1322.26 | 423 | 1228.27 |
| | W-135 | 423 | 1407.22 | 423 | 1544.99 |
| **Geometric mean fold-rise in antibody titers** | A | 423 | 44.92 | 423 | 31.43 |
| | C | 423 | 43.83 | 423 | 34.17 |
| | Y | 423 | 11.62 | 423 | 10.16 |
| | W-135 | 423 | 51.98 | 423 | 51.47 |
| **Percentage of participants seroconverting† (Day 0 titer < 1:8 and Day 28 titer ≥ 1:32)** | A | 81 | 100.00 | 93 | 100.00 |
| | C | 155 | 98.71 | 152 | 99.34 |
| | Y | 61 | 98.36 | 47 | 100.00 |
| | W-135 | 164 | 98.17 | 139 | 99.28 |
| **Percentage of participants with Day 28 titer ≥ 1:128** | A | 423 | 99.76 | 423 | 100.00 |
| | C | 423 | 98.82 | 423 | 98.35 |
| | Y | 423 | 99.53 | 423 | 99.29 |
| | W-135 | 423 | 98.58 | 423 | 98.82 |

$N_T$ and $N_M$ represent the total number of participants for whom the immune response criterion was calculated (who had valid serology data) in the Menactra vaccine and Menomune vaccine groups, respectively.

**Table 10: Study MTA02, Descriptive Immunogenicity Results: IgG Concentrations (µg/mL) (Per-protocol Population)**

| | | Menactra Vaccine | | Menomune Vaccine | |
|---|---|---|---|---|---|
| **Immune Response Parameter** | **Serogroup** | **$N_T$*** | **% or Titer** | **$N_M$*** | **% or Titer** |
| **Geometric mean concentration on Day 0** | A | 82 | 0.84 | 79 | 0.62 |
| | C | 82 | 0.27 | 79 | 0.30 |
| | Y | 82 | 0.41 | 79 | 0.39 |
| | W-135 | 82 | 0.24 | 79 | 0.24 |
| **Geometric mean concentration on Day 28** | A | 82 | 18.09 | 79 | 11.61 |
| | C | 82 | 5.54 | 79 | 8.08 |
| | Y | 82 | 4.41 | 79 | 9.17 |
| | W-135 | 82 | 2.95 | 79 | 4.93 |
| **Geometric mean fold-rise in antibody concentration** | A | 82 | 21.49 | 79 | 18.87 |
| | C | 82 | 20.78 | 79 | 26.97 |
| | Y | 82 | 10.81 | 79 | 23.55 |
| | W-135 | 82 | 12.26 | 79 | 20.40 |

N τ and $N_M$ represent the total number of participants for whom the immune response criterion was calculated (who had valid serology data) in the Menactra vaccine and Menomune vaccine groups, respectively.

**Table 11: Study MTA02, Descriptive Immunogenicity Results: IgM Titers (Per-protocol Population)**

| | | Menactra Vaccine | | Menomune Vaccine | |
|---|---|---|---|---|---|
| **Immune Response Parameter** | **Serogroup** | **$N_T$*** | **% or Titer** | **$N_M$*** | **% or Titer** |
| **Geometric mean concentration on Day 0** | A | 81 | 1.66 | 79 | 1.42 |
| | C | 82 | 0.19 | 79 | 0.16 |
| | Y | 82 | 0.37 | 79 | 0.40 |
| | W-135 | 82 | 0.17 | 79 | 0.18 |
| **Geometric mean concentration on Day 28** | A | 80 | 17.80 | 79 | 12.00 |
| | C | 80 | 1.55 | 79 | 1.71 |
| | Y | 80 | 3.47 | 79 | 3.45 |
| | W-135 | 82 | 1.92 | 79 | 1.68 |
| **Geometric mean fold-rise in antibody concentration** | A | 79 | 11.22 | 79 | 8.47 |
| | C | 80 | 8.42 | 79 | 10.60 |
| | Y | 80 | 9.47 | 79 | 8.65 |
| | W-135 | 82 | 11.01 | 79 | 9.16 |

**N τ and $N_M$ represent the total number of participants for whom the immune response criterion was calculated (who had valid serology data) in the Menactra vaccine and Menomune vaccine groups, respectively.**

### *Study MTA12*

The study population consisted of 1019 participants who were randomized to one of two treatment groups. The treatments administered to each group are summarised below. The vaccination schedules of Group A and Group B were:

- ***Group A***: Td vaccine and Menactra vaccine on Day 0 (Visit 1) and placebo (saline) on Day 28 (Visit 2).
- ***Group B***: Td vaccine and placebo on Day 0 (Visit 1) and Menactra vaccine on Day 28 (Visit 2).

There were a total of three visits, two vaccination visits, followed by a final third visit at which blood was collected. Participants in this trial were aged from 11 to 17 years. Blood was collected from all participants before vaccination on Day 0 and before and after vaccination on Day 28 for assessment of antibody to each of the vaccines.

The study included similar numbers of females and males (48.8-49.3% compared to 50.9-51.2%, respectively), the mean and median ages of the participants were 12.9 and 12.0-13.0, respectively (the range was 10-17 years). The majority of subjects were Caucasian (89.4-90.2%) with smaller numbers of Black (4.7-4.9%) and Hispanic participants (2.1-3.1%). A smaller number of Asian (0.4-0.6%) and Other (2.0-2.5%) were also included. The baseline distributions of participants by sex, age, and race were not statistically different between the two treatment groups (p-values: 0.900, 0.497 and 0.824 respectively). SBA-BR antibody titres results are described in Table 12.

**Table 12: Study MTA12 Immunogenicity Results: SBA-BR Antibody Titers (PP Population)**

| | | Group A* | | Group B† | |
|---|---|---|---|---|---|
| Immune Response Parameter | Serogroup | N‡ | % or Titer | N* | % or Titer |
| Percentage of participants with ≥ 4-fold rise | A | 465 | 90.11 | 478 | 90.59 |
| | C | 465 | 91.18 | 478 | 82.43 |
| | Y | 465 | 85.81 | 478 | 65.06 |
| | W-135 | 465 | 96.34 | 478 | 87.66 |
| Geometric mean titer on Day 28 | A | 466 | 11312.8 | 478 | 10391.4 |
| | C | 466 | 5059.3 | 478 | 2136.0 |
| | Y | 466 | 3390.9 | 478 | 1331.3 |
| | W-135 | 466 | 4194.7 | 478 | 1339.1 |

Group A: Td + Menactra vaccine, then placebo. Group B: Td + placebo, then Menactra vaccine. N represents the total number of participants for whom the immune response criterion was calculated (who had valid serology data) in each group.

*Assessment of Study Primary Hypothesis 1:*

The non-inferiority hypothesis was defined by the upper limit of the two-sided 95% CI of the difference *P*Td + Placebo - *P*Td + Menactra < 0.1, where *P*Td + Placebo and *P*Td + Menactra where the proportions of participants with acceptable antibody titres in the group receiving Td vaccine with placebo (Group B) and the group receiving Menactra vaccine concomitantly with Td vaccine (Group A), respectively, for each of the diphtheria and tetanus titres. Two hypotheses were tested, one for diphtheria and one for tetanus titres. The differences in the proportions were 2.60% and - 4.03% for tetanus and diphtheria antigens, respectively, and the upper limits of the two-sided 95% CIs of the differences between these proportions were 6.82% for tetanus and - 2.07% for diphtheria. These limits

were below the non-inferiority margin of 10%. Based on these results, non-inferiority was concluded using 10% as a non-inferiority margin and Type 1 error rate of $\alpha = 0.025$.

*Assessment of Study Primary Hypothesis 2:*

This non-inferiority hypothesis was defined by the upper limit of the two-sided 95% CI of *P*Menactra - *P*Td+Menactra < 0.1, where *P*Menactra was the proportion of participants with at least a 4-fold rise in antibody titre in the group receiving Td vaccine followed by Menactra vaccine (Group B), and *P*Td+Menactra was the proportion of participants with at least a 4-fold rise in antibody titre in the group receiving Menactra vaccine concomitantly with Td vaccine (Group A).

The differences in the proportions were 0.48%, - 8.76%, - 20.74% and 8.69% for serogroups A, C, Y, and W-135, respectively. The upper limits of the two-sided 95% CIs of the differences between these proportions were 4.25%, - 4.48%, -15.42% and - 5.28% for serogroups A, C, Y, and W-135, respectively. These limits were below the non-inferiority margin of 10%. Based on these results, the non-inferiority was concluded using 10% as a non-inferiority margin and Type 1 error rate of $\alpha = 0.025$.

*Assessment of Study Secondary Hypothesis 3:*

This non-inferiority hypothesis was defined by the upper limit of the two-sided 95% CI of the ratio SBA-BR GMT Menactra / GMT Td + Menactra < 2, where GMT Menactra and GMT Td + Menactra were the GMTs of the serogroups A, C, Y, and W-135 in the group of participants receiving Menactra vaccine following Td vaccine 28 days later (Group B) and in the group receiving Td vaccine + Menactra vaccine concomitantly (Group A). The GMT ratios were 0.92, 0.42, 0.39, and 0.32 for serogroups A, C, Y, and W-135, respectively, and the upper limits of the two-sided 95% CIs for the GMT ratios were 1.1, 0.5, 0.5, and 0.4 for serogroups A, C, Y, and W-135, respectively. These limits were below the non-inferiority margin of 2. Based on these results, non-inferiority was concluded using 10% as a non-inferiority margin and Type 1 error rate of $\alpha = 0.025$.

*Summary of Study MTA12:*

- The immunogenic response to Menactra vaccine when given concomitantly with Td vaccine was non-inferior to the response when Menactra vaccine was given 28 days following Td vaccine, in the adolescent population.
- The immunogenic response to the Td vaccine when given concomitantly with Menactra vaccine was non-inferior to the response when Td vaccine was given with placebo in the adolescent population.
- There was no observed negative interference to the antibody response to Td vaccine or to Menactra vaccine when these vaccines were given concomitantly.
- Antibody levels to diphtheria and to serogroups C, Y, and W-135 polysaccharides were enhanced when Menactra vaccine was given concomitantly with Td vaccine.

### *Studies in Children*

#### *Study 603-02*

The study population consisted of 1398 participants (aged 2 to 10 years) who were randomized to receive a single injection of either Menactra vaccine or Menomune vaccine. No concomitant vaccines were administered. Blood specimens obtained on Day 0 prior to vaccination (baseline), on Day 28 post-vaccination, and at 6 months after vaccination were assayed for meningococcal serogroups A, C, Y, and W-135 antibodies.

The study included a similar number of males and females (51.9-52.7% and 47.3-48.1%, respectively), the mean and median ages of the participants were 3.6-3.7and 3.0 years, respectively (the range was 2-10 years). The majority of subjects were Caucasian (90.2-90.5%) with smaller numbers of Black (4.0%) and Hispanic participants (1.1-1.3%). A smaller number of Asian (0.4%) and Other (3.9-4.1%) were also included. The baseline distributions of participants by sex, age, and race were not statistically different between the two treatment groups. Tables 13-15 describe the results of immunogenicity on Day 0 and Day 28 (for the 6-month immunogenicity results, see section *on Persistence of Efficacy*) for SBA-BR, IgG, and IgM titres, respectively.

**Table 13: Study 603-02 Day 0 and Day 28 Immunogenicity Results: SBA-BR Titers (Per-protocol Population)**

| | | Menactra Vaccine | | Menomune Vaccine | |
|---|---|---|---|---|---|
| **Immune Response Parameter** | **Serogroup** | **$N_T$*** | **% or Titer** | **$N_M$*** | **% or Titer** |
| **Percentage of participants with ≥ 4-fold rise** | A | 636 | 87.74 | 654 | 83.79 |
| | C | 635 | 73.39 | 653 | 68.91 |
| | Y | 634 | 56.62 | 653 | 45.64 |
| | W-135 | 635 | 91.02 | 652 | 85.43 |
| **Geometric mean titer on Day 0** | A | 637 | 35.56 | 656 | 32.61 |
| | C | 637 | 20.68 | 656 | 18.67 |
| | Y | 636 | 118.60 | 655 | 117.98 |
| | W-135 | 637 | 12.11 | 655 | 12.13 |
| **Geometric mean titer on Day 28** | A | 637 | 1700.28 | 655 | 893.33 |
| | C | 636 | 353.85 | 654 | 231.23 |
| | Y | 636 | 636.70 | 655 | 408.24 |
| | W-135 | 636 | 749.78 | 654 | 426.23 |
| **Geometric mean fold-rise in antibody titers (from Day 0 to Day 28)** | A | 636 | 35.18 | 654 | 20.29 |
| | C | 635 | 11.86 | 653 | 8.44 |
| | Y | 634 | 4.83 | 653 | 3.13 |
| | W-135 | 635 | 40.24 | 652 | 23.09 |
| **Percentage of participants seroconverting† (Day 0 titer < 1:8 and Day 28 titer ≥ 1:32)** | A | 279 | 98.57 | 281 | 94.66 |
| | C | 338 | 87.87 | 366 | 80.05 |
| | Y | 87 | 86.21 | 96 | 75.00 |
| | W-135 | 400 | 96.00 | 402 | 89.55 |
| **Percentage of participants with Day 28 titer ≥ 1:128** | A | 637 | 96.86 | 655 | 92.98 |
| | C | 636 | 81.45 | 654 | 73.39 |
| | Y | 636 | 92.77 | 655 | 86.09 |
| | W-135 | 636 | 90.88 | 654 | 86.09 |

$N_\tau$ and $N_M$ represent the total number of participants for whom the immune response criterion was calculated (that is, who had valid serology data) in the Menactra vaccine and Menomune vaccine groups, respectively.

**Table 14: Study 603-02 Immunogenicity Results. IgG Concentrations (µg/mL) (PP Population)**

| | | Menactra Vaccine | | Menomune Vaccine | |
|---|---|---|---|---|---|
| Immune Response Parameter | Serogroup | $N_T$* | % or Concentration | $N_M$* | % or Concentration |
| Geometric mean concentration on Day 0 | A | 115 | 0.36 | 113 | 0.33 |
| | C | 115 | 0.23 | 113 | 0.25 |
| | Y | 115 | 0.38 | 114 | 0.34 |
| | W-135 | 115 | 0.25 | 113 | 0.22 |
| Geometric mean concentration on Day 28 | A | 115 | 7.65 | 110 | 6.81 |
| | C | 115 | 1.24 | 110 | 7.62 |
| | Y | 115 | 1.54 | 110 | 4.15 |
| | W-135 | 115 | 0.90 | 110 | 2.53 |
| Geometric mean fold-rise in antibody concentration (from Day 0 to Day 28) | A | 115 | 21.00 | 108 | 21.09 |
| | C | 115 | 5.50 | 109 | 30.18 |
| | Y | 115 | 4.04 | 109 | 12.43 |
| | W-135 | 115 | 3.60 | 108 | 11.67 |

$N_T$ and $N_M$ represent the total number of participants for whom the immune response criterion was calculated (who had valid serology data) in the Menactra and Menomune vaccine groups, respectively.

**Table 15: Study 603-02 Immunogenicity Results: IgM Concentrations (µg/mL) (PP Population)**

| | | Menactra Vaccine | | Menomune Vaccine | |
|---|---|---|---|---|---|
| Immune Response Parameter | Serogroup | $N_T$* | % or Concentration | $N_M$* | % or Concentration |
| Geometric mean concentration on Day 0 | A | 113 | 0.64 | 108 | 0.61 |
| | C | 113 | 0.10 | 108 | 0.09 |
| | Y | 113 | 0.35 | 107 | 0.34 |
| | W-135 | 113 | 0.15 | 107 | 0.14 |
| Geometric mean concentration on Day 28 | A | 112 | 4.20 | 108 | 2.78 |
| | C | 112 | 0.28 | 108 | 0.39 |
| | Y | 111 | 1.17 | 107 | 0.69 |
| | W-135 | 111 | 0.52 | 108 | 0.30 |
| Geometric mean fold-rise in antibody concentration (from Day 0 to Day 28) | A | 112 | 5.89 | 108 | 4.31 |
| | C | 112 | 1.94 | 108 | 2.92 |
| | Y | 111 | 2.73 | 106 | 1.69 |
| | W-135 | 111 | 1.87 | 107 | 1.11 |

$N_T$ and $N_M$ represent the total number of participants for whom the immune response criterion was calculated (who had valid serology data) in the Menactra and Menomune vaccine groups, respectively.

*Assessment of Study Primary Hypothesis:*

To demonstrate the non-inferiority of Menactra vaccine to Menomune vaccine the following criteria had to hold simultaneously for the four serogroups on Day 28: For serogroups A, C, Y, and W-135, the upper limit of the one-sided 95% CI of *p*Menomune – *p*Menactra was <0.10, where *p* represented the proportion of participants with a ≥ 4-fold rise in SBA-BR

titre from baseline. For each serogroup, these percentages were higher in the Menactra group than in the Menomune vaccine group. The differences in the percentages (*p*Menomune - *p*Menactra) were -3.94%, -4.47%, -10.99%, and -5.59% for serogroups A, C, Y, and W-135, respectively. The upper limits of the one-sided 95% CIs of these differences were -0.75%, -0.33%, -6.43%, and -2.65% for serogroups A, C, Y, and W-135, respectively; which were below the non-inferiority margin of 10%. Based on these results, non-inferiority was concluded using 10% as a non-inferiority margin and Type 1 error rate of $\alpha = 0.05$.

***Study MTA17 Stage I***

The study population consisted of 171 participants (aged 4 to 6 years) who received a single injection of reduced dose (1/10) of Menomune vaccine. No concomitant vaccines were administered. The Menactra vaccine-primed subjects had received the priming dose of Menactra vaccine on average 28.4 months (range from 23 to 36 months) before receiving the challenge dose of Menomune vaccine. Blood specimens obtained on Day 0 prior to vaccination (baseline), and alternatively on either Day 8 or Day 28 post-vaccination, were assayed for meningococcal serogroups A, C, Y, and W-135 antibodies. No statistical hypotheses were tested.

The ratio of male to female participants was higher in the Menactra group compared to the control subjects (58% males and 38% males, respectively). The mean and median ages were 3.8-4.5 years and 4.0 years, respectively (range 3-5 years in both groups). The majority of subjects were Caucasian (85.9-92.0%) with smaller numbers of Black (2.0-7.0) and Hispanic participants (1.4-2.0%). A smaller number of Asian (0-1.09%) and Other (3.0-5.6%) were also included.

The baseline distributions of participants by sex and age were statistically different between the two study groups. The Control group had a significantly ($p = 0.013$) different gender distribution with fewer males (38.0%) and a significantly higher percentage ($p < 0.001$) of younger participants (mean age of 3.8 years) compared to the Menactra vaccine-primed participants (58.0% male, mean age of 4.5 years). For both study groups, however, the age range was comparable. The baseline distributions of participants by race were not statistically different between the two study groups. Tables 16-18 describe the results of immunogenicity on Day 0, Day 8, and Day 28 for SBA-BR titres, IgG antibody concentrations and avidity indices, respectively.

**Table 16: Study MTA17 Stage I Immunogenicity Results: SBA-BR Titers (Per-protocol Population)**

| | | Menactra Vaccine Primed Subjects | | Meningococcal Vaccine-Naïve Control Subjects | |
|---|---|---|---|---|---|
| **Immune Response Parameter** | **Serogroup** | **$N_T$*** | **% or Titer** | **$N_C$*** | **% or Titer** |
| **Geometric mean titer on Day 0** | A | 92 | 316.12 | 61 | 126.55 |
| | C | 92 | 68.49 | 61 | 21.26 |
| | Y | 92 | 411.51 | 61 | 241.86 |
| | W-135 | 92 | 92.58 | 61 | 17.52 |
| **Geometric mean titer on Day 8** | A | 46 | 11411.97 | 35 | 6720.19 |
| | C | 46 | 8700.95 | 35 | 2447.58 |
| | Y | 46 | 7261.68 | 35 | 3859.73 |
| | W-135 | 46 | 11761.13 | 35 | 5194.82 |
| **Geometric mean titer on Day 28** | A | 46 | 5620.65 | 26 | 2603.35 |
| | C | 46 | 7261.68 | 26 | 300.41 |
| | Y | 46 | 3798.74 | 26 | 1410.06 |
| | W-135 | 46 | 6245.91 | 26 | 2103.33 |
| **Percentage of participants with Day 0 titer ≥ 1:128** | A | 92 | 75.00 | 61 | 68.85 |
| | C | 92 | 52.17 | 61 | 29.51 |
| | Y | 92 | 90.22 | 61 | 70.49 |
| | W-135 | 92 | 60.87 | 61 | 22.95 |
| **Percentage of participants with Day 8 titer ≥ 1:128** | A | 46 | 100.00 | 35 | 100.00 |
| | C | 46 | 100.00 | 35 | 100.00 |
| | Y | 46 | 100.00 | 35 | 100.00 |
| | W-135 | 46 | 100.00 | 35 | 100.00 |
| **Percentage of participants with Day 28 titer ≥ 1:128** | A | 46 | 100.00 | 26 | 100.00 |
| | C | 46 | 100.00 | 26 | 80.77 |
| | Y | 46 | 100.00 | 26 | 100.00 |
| | W-135 | 46 | 100.00 | 26 | 100.00 |

$N_\tau$ and $N_c$ represent the total number of participants for whom the immune response criterion was calculated (who had valid serology data) in the Menactra vaccine-primed and Control groups, respectively.

**Table 17: Study MTA17 Stage I Immunogenicity Results: IgG Concentrations (µg/mL) (Per-protocol Population)**

| | | Menactra Vaccine-Primed Subjects | | Meningococcal Vaccine-Naïve Control Subjects | |
|---|---|---|---|---|---|
| **Immune Response Parameter** | **Serogroup** | **$N_T$*** | **GMC** | **$N_C$*** | **GMC** |
| **Geometric mean concentration on Day 0** | A | 92 | 0.92 | 61 | 0.44 |
| | C | 92 | 0.30 | 61 | 0.28 |
| | Y | 92 | 0.72 | 61 | 0.51 |
| | W-135 | 92 | 0.30 | 61 | 0.32 |
| **Geometric mean concentration on Day 8** | A | 46 | 13.90 | 34 | 4.43 |
| | C | 46 | 8.78 | 35 | 2.48 |
| | Y | 46 | 21.98 | 34 | 3.20 |
| | W-135 | 46 | 11.15 | 34 | 1.24 |
| **Geometric mean concentration on Day 28** | A | 46 | 11.87 | 26 | 3.40 |
| | C | 46 | 7.65 | 26 | 2.74 |
| | Y | 46 | 26.14 | 26 | 3.82 |
| | W-135 | 46 | 17.93 | 26 | 2.27 |

$N_\tau$ and $N_c$ represent the total number of participants for whom the immune response criterion was calculated (who had valid serology data) in the two groups, respectively.

**Table 18: Study MTA17 Stage I Immunogenicity Results: Geometric Mean Avidity Indices (GMAI) (Per-protocol Population)**

| | | Menactra Vaccine-Primed Subjects | | Meningococcal Vaccine-Naïve Control Subjects | |
|---|---|---|---|---|---|
| **Immune Response Parameter** | **Serogroup** | **$N_T$*** | **GMAI** | **$N_C$*** | **GMAI** |
| **Geometric mean avidity indices on Day 0** | A | 33 | 190.22 | 7 | 141.23 |
| | C | 9 | 187.03 | 4 | 91.42 |
| | Y | 29 | 235.57 | 9 | 139.63 |
| | W-135 | 3 | 157.72 | 5 | 209.49 |
| **Geometric mean avidity indices on Day 8** | A | 41 | 363.05 | 30 | 140.50 |
| | C | 41 | 290.56 | 18 | 112.48 |
| | Y | 38 | 320.96 | 28 | 135.50 |
| | W-135 | 41 | 470.14 | 17 | 162.97 |
| **Geometric mean avidity indices on Day 28** | A | 37 | 404.89 | 18 | 131.71 |
| | C | 42 | 323.74 | 14 | 106.94 |
| | Y | 45 | 383.64 | 24 | 130.06 |
| | W-135 | 46 | 483.10 | 18 | 195.64 |

$N_\tau$ and $N_c$ represent the total number of participants for whom the immune response criterion was calculated (who had valid serology data) in the two groups, respectively.

*Summary of Study MTA17:*

- Young children primed with Menactra vaccine had persistent serum bactericidal antibody activity to all four serogroups approximately two years after a single priming dose of vaccine.

- An immune memory response and evidence of antibody avidity maturation was demonstrated using a low dose of polysaccharide antigen in conjugate-primed subjects.

***Study MTA08***

The study population was healthy children aged ≥ 2 to < 11 years who met all of the inclusion criteria and none of the exclusion criteria. Eligible participants were randomized to receive a single injection of either Menactra vaccine or Menomune vaccine. No concomitant vaccines were administered with the trial products. For the subset of Chilean Menactra vaccine and Menomune vaccine recipients, blood samples were collected at baseline (Day 0 prior to vaccination) and at Day 28 post vaccination for immunogenicity assessments.

The baseline distributions of participants by sex, age, and race were not statistically different between the two treatment groups. Participants ranged in age from 2 to 10 years (mean age: 3.7 years). There were 52.3% males and 47.7% females. The majority (90.3%) of participants were Caucasian. The Chilean participants were younger (median 5.0 years) than the US participants (median 6.0 years). Table 19 and Table 20 describe the results of immunogenicity on Day 0 and Day 28 for SBA-BR titres and IgG concentrations, respectively, obtained in the sub-sample of Chilean participants randomized to contribute to this observational objective.

**Table 19: Study MTA08, Descriptive Immunogenicity Results: SBA-BR Titers (Per-protocol Population - Chilean subjects)**

| | | Menactra Vaccine | | Menomune Vaccine | |
|---|---|---|---|---|---|
| **Immune Response Parameter** | **Serogroup** | **$N_T$*** | **% or Titer** | **$N_M$*** | **% or Titer** |
| **Percentage of participants with ≥ 4-fold rise** | A | 119 | 77.31 | 98 | 77.55 |
| | C | 119 | 82.35 | 98 | 77.55 |
| | Y | 119 | 68.07 | 98 | 66.33 |
| | W-135 | 119 | 92.44 | 98 | 89.80 |
| **Geometric mean titer on Day 0** | A | 119 | 84.2 | 98 | 86.1 |
| | C | 119 | 47.3 | 98 | 59.2 |
| | Y | 119 | 497.3 | 98 | 460.5 |
| | W-135 | 119 | 36.6 | 98 | 36.9 |
| **Geometric mean titer on Day 28** | A | 119 | 2108.5 | 98 | 1644.8 |
| | C | 119 | 1164.0 | 98 | 1222.1 |
| | Y | 119 | 2615.6 | 98 | 2019.2 |
| | W-135 | 119 | 1226.6 | 98 | 1154.8 |
| **Geometric mean fold-rise in antibody titers (Day 28)** | A | 119 | 20.1 | 98 | 15.3 |
| | C | 119 | 19.2 | 98 | 16.6 |
| | Y | 119 | 5.2 | 98 | 4.3 |
| | W-135 | 119 | 26.9 | 98 | 25.3 |
| **Percentage of participants seroconverting (Day 0 titer < 1:8 and Day 28 titer ≥ 1:32)** | A | 38 | 97.37 | 31 | 100.00 |
| | C | 43 | 100.00 | 31 | 90.32 |
| | Y | 3 | 100.00 | 3 | 100.00 |
| | W-135 | 38 | 97.37 | 30 | 100.00 |

$N_\tau$ and $N_M$ represent the total number of participants for whom the immune response criterion was calculated (that is, who had valid serology data) in the Menactra vaccine and Menomune vaccine groups, respectively.

**Table 20: Study MTA08 Descriptive Immunogenicity Results: IgG Concentrations (µg/mL) (PP Population - Chilean subjects)**

| | | Menactra Vaccine | | Menomune Vaccine | |
|---|---|---|---|---|---|
| Immune Response Parameter | Serogroup | $N_T$* | % or Concentration | $N_M$* | % or Concentration |
| Geometric mean concentration on Day 0 | A | 119 | 0.9 | 98 | 0.8 |
| | C | 119 | 0.3 | 98 | 0.5 |
| | Y | 119 | 0.7 | 98 | 0.7 |
| | W-135 | 119 | 0.2 | 98 | 0.2 |
| Geometric mean concentration on Day 28 | A | 119 | 20.7 | 98 | 19.9 |
| | C | 119 | 3.4 | 98 | 17.0 |
| | Y | 119 | 7.1 | 98 | 20.5 |
| | W-135 | 119 | 2.4 | 98 | 7.5 |
| Geometric mean fold-rise in antibody concentration (Day 28) | A | 119 | 18.9 | 98 | 19.7 |
| | C | 119 | 7.0 | 98 | 25.8 |
| | Y | 119 | 7.7 | 98 | 22.9 |
| | W-135 | 119 | 6.9 | 98 | 22.9 |

$N_\tau$ and $N_M$ represent the total number of participants for whom the immune response criterion was calculated (who had valid serology data) in the Menactra vaccine and Menomune vaccine groups, respectively.

No formal statistical comparisons were performed during this trial, as it was a purely descriptive study.

*Summary of Study MTA08:*

Based on the observations of immunogenicity in the nested Chilean study, Menactra vaccine was found to be highly immunogenic in this population of children aged 2 to <11 years.

### *Study MTA15*

The study population was healthy children aged ≥ 2 to < 6 years. Eligible participants were randomized to receive a single injection of either Menactra vaccine or Hiberix® (*H influenzae* type b tetanus conjugated vaccine). No concomitant vaccines were administered with the trial products. Blood samples were collected at baseline (Day 0) prior to vaccination and at Day 28 postvaccination for immunogenicity assessments.

Participants ranged in age from 2 to almost 6 years (mean age: 3 years). There were 46.2-56.93% males and 43.1-53.8% females. The majority of participants were Caucasian (42.3-51.0%) or Asian (41.2-42.3%). The baseline distributions of participants by sex, age, and race were not statistically different between the two treatment groups. Tables 21 and 22 describe the results of immunogenicity on Day 0 and Day 28 for SBA-BR and IgG titres, respectively.

**Table 21: Study MTA15 Descriptive Immunogenicity Results: SBA-BR Titers (PP Population)**

| | | Menactra Vaccine | | Hiberix Vaccine | |
|---|---|---|---|---|---|
| **Immune Response Parameter** | **Serogroup** | **$N_T$*** | **% or Titer** | **$N_C$*** | **% or Titer** |
| **Percentage of participants with ≥ 4-fold rise** | A | 44 | 97.73 | 36 | 30.56 |
| | C | 44 | 93.18 | 36 | 5.56 |
| | Y | 44 | 79.55 | 36 | 2.78 |
| | W-135 | 44 | 97.73 | 36 | 22.22 |
| **Geometric mean titer on Day 0** | A | 44 | 136.33 | 36 | 99.66 |
| | C | 44 | 76.11 | 36 | 26.91 |
| | Y | 44 | 236.61 | 36 | 266.05 |
| | W-135 | 44 | 26.07 | 36 | 24.44 |
| **Geometric mean titer on Day 28** | A | 44 | 11404.16 | 36 | 199.31 |
| | C | 44 | 12534.67 | 36 | 22.63 |
| | Y | 44 | 4031.98 | 36 | 298.63 |
| | W-135 | 44 | 5978.03 | 36 | 32.00 |
| **Geometric mean fold-rise in antibody titers (Day 28)** | A | 44 | 70.34 | 36 | 1.65 |
| | C | 44 | 136.33 | 36 | 0.57 |
| | Y | 44 | 16.51 | 36 | 1.06 |
| | W-135 | 44 | 159.59 | 36 | 0.91 |

$N_T$ and $N_C$ represent the total number of participants for whom the immune response criterion was calculated (who had valid serology data) in the Menactra vaccine and control groups, respectively.

**Table 22: Study MTA15. Descriptive Immunogenicity Results: IgG Concentrations (µg/mL) (Per-protocol Population)**

| | | Menactra Vaccine | | Hiberix Vaccine | |
|---|---|---|---|---|---|
| **Immune Response Parameter** | **Serogroup** | **$N_T$*** | **% or Concentration** | **$N_M$*** | **% or Concentration** |
| **Geometric mean concentration on Day 0** | A | 44 | 0.82 | 36 | 0.63 |
| | C | 44 | 0.44 | 36 | 0.43 |
| | Y | 44 | 0.45 | 36 | 0.33 |
| | W-135 | 44 | 0.33 | 36 | 0.23 |
| **Geometric mean concentration on Day 28** | A | 44 | 25.75 | 35 | 0.69 |
| | C | 44 | 9.56 | 35 | 0.41 |
| | Y | 44 | 7.83 | 35 | 0.35 |
| | W-135 | 44 | 9.02 | 35 | 0.20 |
| **Geometric mean fold-rise in antibody concentration (Day 28)** | A | 44 | 26.74 | 35 | 0.89 |
| | C | 44 | 15.86 | 35 | 0.74 |
| | Y | 44 | 12.13 | 35 | 0.63 |
| | W-135 | 44 | 22.00 | 35 | 0.62 |

$N_T$ and $N_M$ represent the total number of participants for whom the immune response criterion was calculated (who had valid serology data) in the Menactra vaccine and control groups, respectively.

*Assessment of Study Primary Hypothesis:*

The hypothesis tested that 28 days after vaccination, Menactra-vaccinated participants were superior to Hiberix-vaccinated participants by the proportion of participants with a ≥4-fold rise in their SBA-BR titres for *N. meningitidis* serogroup C. To demonstrate the superiority of Menactra vaccine to Hiberix vaccine on Day 28 for serogroup C, the lower limit of the one-sided 95% CI of *p*Menactra. *p*Hiberix had to be > 0.50, where *p* represented

the proportion of participants with a ≥ 4-fold rise in SBA-BR titre from baseline. For serogroup C, the percentage was higher in the Menactra vaccine group than in the Hiberix vaccine group. The difference in the percentages (*p*Menactra - *p*Hiberix) was 87.63%, and the lower limit of the one-sided 95% CI of this difference was 78.77% and hence above the superiority margin of 50%. Based on these results, superiority of the vaccine was concluded.

*Summary of Study MTA15:*

• Menactra vaccine was highly immunogenic for all four serogroups contained in the vaccine.

• Menactra vaccine can be used to boost the serogroup C antibody responses in subjects primed with a monovalent meningococcal C conjugate vaccine.

### *Persistence of Efficacy*

Study 603-02 documented the persistence of vaccine-induced antibodies in children (as measured by SBA-BR, IgG, and IgM) after priming with Menactra vaccine up to 6 months after initial priming. The results are presented below (Table 23, Table 24, and Table 25). Study MTA17 Stage I, performed in a subset of children primed with Menactra vaccine, documented:

1) the persistence of vaccine-induced antibodies (as measured by SBA-BR, IgG) 2 to 3 years after their priming,

and

2) their ability to mount a rapid anamnestic antibody response upon stimulation with a low dose (one tenth) of unconjugated polysaccharides versus the responses observed in vaccination-naïve age matched children.

**Table 23: Study 603-02, SBA-BR Geometric Mean Titers at Baseline, Day 28, and Month 6, and Geometric Mean Fold Rises in SBA-BR Titers from Baseline to Day 28 and from Baseline to Month 6 (Per-protocol Population)**

| Serogroup | Parameter | Bleed | Menactra Vaccine | | | Menomune Vaccine | | |
|---|---|---|---|---|---|---|---|---|
| | | | N* | GMT or Geometric Mean Fold Rise† | 95% CI | N* | GMT or Geometric Mean Fold Rise† | 95% CI |
| A | GMT | Day 0 | 637 | 35.56 | 29.86, 42.35 | 656 | 32.61 | 27.63, 38.50 |
| | | Day 28 | 637 | 1700.28 | 1512.08, 1911.90 | 655 | 893.33 | 791.10, 1008.78 |
| | | Month 6 | 607 | 1053.65 | 912.93, 1216.07 | 624 | 215.75 | 180.52, 257.86 |
| | Geometric Mean Fold Rise† | Day 28 | 636 | 35.18 | 29.72, 41.65 | 654 | 20.29 | 17.49, 23.53 |
| | | Month 6 | 607 | 23.19 | 19.20, 28.00 | 623 | 5.07 | 4.24, 6.07 |
| C | GMT | Day 0 | 637 | 20.68 | 17.63, 24.27 | 656 | 18.67 | 15.94, 21.87 |
| | | Day 28 | 636 | 353.85 | 307.95, 406.58 | 654 | 231.23 | 198.21, 269.77 |
| | | Month 6 | 607 | 136.92 | 116.40, 161.06 | 624 | 65.58 | 54.71, 78.61 |
| | Geometric Mean Fold Rise† | Day 28 | 635 | 11.86 | 10.19, 13.81 | 653 | 8.44 | 7.26, 9.81 |
| | | Month 6 | 607 | 4.49 | 3.85, 5.25 | 623 | 2.42 | 2.06, 2.84 |
| Y | GMT | Day 0 | 636 | 118.60 | 102.45, 137.29 | 655 | 117.98 | 102.12, 136.31 |
| | | Day 28 | 636 | 636.70 | 563.06, 719.97 | 655 | 408.24 | 362.38, 459.91 |
| | | Month 6 | 608 | 591.77 | 514.65, 680.43 | 623 | 240.00 | 205.64, 280.10 |
| | Geometric Mean Fold Rise† | Day 28 | 634 | 4.83 | 4.25, 5.49 | 653 | 3.13 | 2.79, 3.52 |
| | | Month 6 | 607 | 4.63 | 4.00, 5.37 | 621 | 1.85 | 1.60, 2.15 |
| W-135 | GMT | Day 0 | 637 | 12.11 | 10.64, 13.79 | 655 | 12.13 | 10.67, 13.78 |
| | | Day 28 | 636 | 749.78 | 657.37, 855.18 | 654 | 426.23 | 372.77, 487.34 |
| | | Month 6 | 607 | 362.25 | 311.67, 421.03 | 625 | 136.66 | 118.59, 157.47 |
| | Geometric Mean Fold Rise† | Day 28 | 635 | 40.24 | 34.30, 47.21 | 652 | 23.09 | 19.83, 26.89 |
| | | Month 6 | 607 | 19.19 | 16.31, 22.56 | 623 | 7.46 | 6.37, 8.74 |

N: number of participants with valid serology data. Geometric mean fold rise = geometric mean of (titre at Day 28 or Month 6)/Titre at Day 0.

**Table 24: Study 603-02 IgG Geometric Mean Concentrations at Baseline, Day 28, and Month 6, and Geometric Mean Fold Rises in IgG Concentrations from Baseline to Day 28 and from Baseline to Month 6 (Subset of the Per-protocol Population)**

| Serogroup | Parameter | Bleed | Menactra Vaccine | | | Menomune Vaccine | | |
|---|---|---|---|---|---|---|---|---|
| | | | N* | GMC or Geometric Mean Fold Rise† | 95% CI | N* | GMC or Geometric Mean Fold Rise† | 95% CI |
| A | GMC (µg/mL) | Day 0 | 115 | 0.36 | 0.31, 0.43 | 113 | 0.33 | 0.28, 0.38 |
| | | Day 28 | 115 | 7.65 | 6.27, 9.33 | 110 | 6.81 | 5.51, 8.42 |
| | | Month 6 | 112 | 1.70 | 1.37, 2.11 | 109 | 4.53 | 3.60, 5.70 |
| | Geometric Mean Fold Rise† | Day 28 | 115 | 21.00 | 16.60, 26.58 | 108 | 21.09 | 16.78, 26.50 |
| | | Month 6 | 112 | 4.58 | 3.65, 5.75 | 107 | 14.40 | 11.22, 18.49 |
| C | GMC (µg/mL) | Day 0 | 115 | 0.23 | 0.20, 0.25 | 113 | 0.25 | 0.22, 0.29 |
| | | Day 28 | 115 | 1.24 | 1.03, 1.50 | 110 | 7.62 | 6.33, 9.19 |
| | | Month 6 | 111 | 0.36 | 0.31, 0.43 | 109 | 3.49 | 2.82, 4.32 |
| | Geometric Mean Fold Rise† | Day 28 | 115 | 5.50 | 4.58, 6.62 | 109 | 30.18 | 24.26, 37.55 |
| | | Month 6 | 111 | 1.60 | 1.36, 1.89 | 107 | 14.42 | 11.46, 18.15 |
| Y | GMC (µg/mL) | Day 0 | 115 | 0.38 | 0.34, 0.43 | 114 | 0.34 | 0.31, 0.38 |
| | | Day 28 | 115 | 1.54 | 1.26, 1.88 | 110 | 4.15 | 3.30, 5.22 |
| | | Month 6 | 112 | 0.76 | 0.65, 0.89 | 109 | 2.90 | 2.25, 3.73 |
| | Geometric Mean Fold Rise† | Day 28 | 115 | 4.04 | 3.30, 4.93 | 109 | 12.43 | 9.85, 15.68 |
| | | Month 6 | 112 | 1.98 | 1.68, 2.32 | 108 | 8.72 | 6.79, 11.21 |
| W-135 | GMC (µg/mL) | Day 0 | 115 | 0.25 | 0.22, 0.28 | 113 | 0.22 | 0.19, 0.25 |
| | | Day 28 | 115 | 0.90 | 0.72, 1.12 | 110 | 2.53 | 2.06, 3.11 |
| | | Month 6 | 112 | 0.55 | 0.47, 0.65 | 109 | 1.88 | 1.53, 2.31 |
| | Geometric Mean Fold Rise† | Day 28 | 115 | 3.60 | 2.90, 4.47 | 108 | 11.67 | 9.34, 14.58 |
| | | Month 6 | 112 | 2.18 | 1.84, 2.58 | 107 | 8.70 | 6.96, 10.87 |

**Table 25: Study 603-02. IgM Geometric Mean Concentrations at Baseline, Day 28, and Month 6, and Geometric Mean Fold Rises in IgM Concentrations from Baseline to Day 28 and from Baseline to Month 6 (Subset of the Per-protocol Population)**

| Serogroup | Parameter | Bleed | Menactra Vaccine | | | Menomune Vaccine | | |
|---|---|---|---|---|---|---|---|---|
| | | | N* | GMC or Geometric Mean Fold Rise† | 95% CI | N* | GMC or Geometric Mean Fold Rise† | 95% CI |
| A | GMC (µg/mL) | Day 0 | 113 | 0.64 | 0.51, 0.81 | 108 | 0.61 | 0.50, 0.74 |
| | | Day 28 | 112 | 4.20 | 3.40, 5.18 | 108 | 2.78 | 2.38, 3.25 |
| | | Month 6 | 112 | 2.46 | 2.01, 3.00 | 107 | 0.8 | 0.65, 0.99 |
| | Geometric Mean Fold Rise† | Day 28 | 112 | 5.89 | 4.83, 7.19 | 108 | 4.31 | 3.73, 4.98 |
| | | Month 6 | 112 | 3.42 | 2.90, 4.05 | 107 | 1.25 | 1.08, 1.43 |
| C | GMC (µg/mL) | Day 0 | 113 | 0.10 | 0.08, 0.11 | 108 | 0.09 | 0.08, 0.10 |
| | | Day 28 | 112 | 0.28 | 0.22, 0.34 | 108 | 0.39 | 0.33, 0.46 |
| | | Month 6 | 112 | 0.17 | 0.14, 0.21 | 107 | 0.13 | 0.11, 0.16 |
| | Geometric Mean | Day 28 | 112 | 1.94 | 1.62, 2.32 | 108 | 2.92 | 2.48, 3.43 |
| | Fold Rise† | Month 6 | 112 | 1.21 | 1.03, 1.42 | 107 | 1.01 | 0.87, 1.17 |
| Y | GMC (µg/mL) | Day 0 | 113 | 0.35 | 0.29, 0.41 | 107 | 0.34 | 0.29, 0.40 |
| | | Day 28 | 111 | 1.17 | 0.96, 1.42 | 107 | 0.69 | 0.58, 0.83 |
| | | Month 6 | 110 | 0.75 | 0.61, 0.91 | 108 | 0.38 | 0.32, 0.46 |
| | Geometric Mean Fold Rise† | Day 28 | 111 | 2.73 | 2.33, 3.20 | 106 | 1.69 | 1.46, 1.95 |
| | | Month 6 | 110 | 1.75 | 1.50, 2.04 | 107 | 0.94 | 0.82, 1.08 |
| W-135 | GMC (µg/mL) | Day 0 | 113 | 0.15 | 0.14, 0.17 | 107 | 0.14 | 0.14, 0.15 |
| | | Day 28 | 111 | 0.52 | 0.43, 0.64 | 108 | 0.30 | 0.26, 0.35 |
| | | Month 6 | 112 | 0.31 | 0.26, 0.38 | 107 | 0.18 | 0.16, 0.20 |
| | Geometric Mean Fold Rise† | Day 28 | 111 | 1.87 | 1.54, 2.27 | 107 | 1.11 | 0.96, 1.28 |
| | | Month 6 | 112 | 1.12 | 0.95, 1.33 | 106 | 0.65 | 0.59, 0.71 |

***Pooled Efficacy Analyses.***

All subjects enrolled in each individual trial were evenly distributed by age, race, and gender. For studies conducted in adults, the populations were very similar in terms of mean age, gender and racial distribution. This was also true for studies conducted in adolescents. Participants enrolled in Study MTA02 were slightly older than participants enrolled in Study MTA11. For studies conducted in children, populations were very similar in terms of gender and racial distributions. The two studies (603-02 and MTA08) which compared the Menactra and the Menomune vaccines enrolled participants that were slightly different in terms of age.

*Studies in Adults*

Table 26 presents the main immunogenicity results (SBA-BR) observed in the adult participants who received Menactra vaccine. The immune responses (the percentage of participants with ≥ 4-fold rise to serogroups A, C, Y, and W-135) were similar in the adult population across the studies.

**Table 26: Menactra Vaccine SBA-BR Results from MTA09, MTA14 Lots 1, 2, and 3, and MTA11 Groups A and B, Aged 18 to 55 Years (Per-protocol Population)**

| Study | Study MTA09 | Study MTA14 | | | Study MTA11 | |
|---|---|---|---|---|---|---|
| Lot number(s) | U0486BA U0486BB | U0566BA | U0567BA | U0568BA | U0566BB | |
| Study group | Menactra Vaccine | Menactra Lot 1 | Menactra Vaccine Lot 2 | Menactra Vaccine Lot 3 | Group A Concomitant Menactra Vaccine + Typhim Vi® | Group B Menactra Vaccine 28 days after Typhim Vi® |
| N for % ≥ 4-fold rise | 1280 | 495 | 486 | 499 | 418 | 419 |
| **Serogroup A** | | | | | | |
| % ≥ 4-fold rise | 80.5% | 85.1% | 85.4% | 81.6% | 79.6% | 75.1% |
| GMT on Day 28 | 3897 | 8169 | 8215 | 6679 | 5138 | 5110 |
| % SC | 100% | 100% | 100% | 100% | 97.7% | 100% |
| **Serogroup C** | | | | | | |
| % ≥ 4-fold rise | 88.5% | 85.9% | 89.5% | 83.2% | 89.4% | 88.3% |
| GMT on Day 28 | 3231 | 3867 | 4155 | 3217 | 3061 | 3145 |
| % SC | 99.4% | 95.7% | 100% | 96.9% | 90.1% | 93.8% |
| **Serogroup Y** | | | | | | |
| % ≥ 4-fold rise | 73.5% | 74.9% | 71.6% | 80.6% | 74.4% | 65.1% |
| GMT on Day 28 | 1750 | 2912 | 2472 | 3805 | 1821 | 1742 |
| % SC | 90.7% | 95.9% | 92.9% | 96.6% | 89.2% | 86.7% |
| **Serogroup W-135** | | | | | | |
| % ≥ 4-fold rise | 89.4% | 86.1% | 88.1% | 91.8% | 85.1% | 83.7% |
| GMT on Day 28 | 1271 | 2031 | 2573 | 2457 | 1002 | 929 |
| % SC | 96.5% | 94.9% | 94.6% | 97.6% | 88.6% | 83.8% |

N = number of participants with valid serology data at Day 0 and Day 28 in each study. % ≥ 4-fold rise refers to the percentage of participants with a ≥ 4-fold-rise in SBA-BR titres on Day 28 from baseline. GMT on Day 28 means geometric mean SBA-BR titre on Day 28. %SC refers to the percentage of participants seroconverting.

*Studies in Adolescents*

Table 27 presents the main immunogenicity results (SBA-BR) observed in the adolescent participants who received Menactra vaccine. The immune responses (percentage of participants with ≥ 4-fold rise to serogroups A, C, Y, and W-135) were similar in adolescents across both studies.

**Table 27: SBA-BR Results from MTA02 and MTA12 Adolescent Group (PP Population)**

| Study | Study MTA02* | Study MTA12* | |
|---|---|---|---|
| Lot number | 0374AA | U0566BB | |
| Study group | Menactra Vaccine | Group A Concomitant Menactra Vaccine +Td Vaccine | Group B Menactra Vaccine 28 days after Td Vaccine |
| N for % ≥ 4-fold rise | 423 | 465 | 478 |
| **Serogroup A** | | | |
| % ≥ 4-fold rise | 92.7% | 90.1% | 90.6% |
| GMT on Day 28 | 5483 | 11313 | 10391 |
| % SC | 100% | 100% | 100% |
| **Serogroup C** | | | |
| % ≥ 4-fold rise | 91.7% | 91.2% | 82.4% |
| GMT on Day 28 | 1924 | 5059 | 2136 |
| % SC | 98.7% | 99.3% | 96.7% |
| **Serogroup Y** | | | |
| % ≥ 4-fold rise | 81.8% | 85.8% | 65.1% |
| GMT on Day 28 | 1322 | 3391 | 1331 |
| % SC | 98.4% | 97.0% | 92.5% |
| **Serogroup W-135** | | | |
| % ≥ 4-fold rise | 96.7% | 96.3% | 87.7% |
| GMT on Day 28 | 1407 | 4195 | 1339 |
| % SC | 98.2% | 99.5% | 96.7% |

Age was 11 to 18 years for Study MTA02 and 11 to 17 years for Study MTA12 N = number of participants with valid serology data at Day 0 and Day 28 in each study. % ≥ 4-fold rise refers to the percentage of participants with a ≥ 4-fold-rise in SBA-BR titres on Day 28 from baseline. GMT on Day 28 means geometric mean SBA-BR titre on Day 28. % SC refers to the percentage of participants who seroconverted.

*Studies in Children*

Table 28 presents the main immunogenicity results (SBA-BR) observed in children who received the Menactra vaccine. Immune responses in children are more age-sensitive than the responses in adults and adolescents. The median age of subjects was lower in Study 603-02 than in the subset evaluated in Study MTA08 and the differences seen in the immune responses reflect this.

**Table 28: SBA-BR Results from Studies 603-02, MTA08 and MTA15, Aged 2 to 10 years (PP Population)**

| Study | Study 603-02 | Study MTA08 | Study MTA15 |
|---|---|---|---|
| Lot numbers | U0282BA | U0566BB | U0915AB and U0915AE |
| Study group | Menactra Vaccine (US) | Menactra Vaccine (Chile) | Menactra Vaccine (UK) |
| N for % ≥ 4-fold rise | 634 | 119 | 44 |
| Serogroup A | | | |
| % ≥ 4-fold rise | 87.74% | 77.31% | 97.73% |
| GMT on Day 28 | 1700.28 | 2108.5 | 11404.16 |
| % SC | 98.57% | 97.37% | NA |
| Serogroup C | | | |
| % ≥ 4-fold rise | 73.39% | 82.35% | 93.18% |
| GMT on Day 28 | 353.85 | 1164.0 | 12534.67 |
| % SC | 87.87% | 100.00% | NA |
| Serogroup Y | | | |
| % ≥ 4-fold rise | 56.62% | 68.07% | 79.55% |
| GMT on Day 28 | 636.70 | 2615.6 | 4031.98 |
| % SC | 86.21% | 100.00% | NA |
| Serogroup W-135 | | | |
| % ≥ 4-fold rise | 91.02% | 92.44% | 97.73% |
| GMT on Day 28 | 749.78 | 1226.6 | 5978.03 |
| % SC | 96.00% | 97.37% | NA |

N = number of participants with valid serology data at Day 0 and Day 28 in each study. % ≥ 4-fold rise refers to the percentage of participants with a ≥ 4-fold-rise in SBA-BR titres on Day 28 from baseline. GMT on Day 28 means geometric mean SBA-BR titre on Day 28. % SC refers to the percentage of participants who seroconverted.

*Randomized Comparative Studies*

Three of the studies in the clinical development program had either primary (Study MTA02 and Study 603-02) or primary and secondary (Study MTA09) objectives of immunogenicity comparisons between Menactra vaccine and Menomune vaccine. The three studies met their primary and secondary objectives, that is, they demonstrated a non-inferiority of the Menactra vaccine immune responses compared to the Menomune vaccine immune responses. Three studies (MTA09, MTA14, and MTA11) were performed in healthy adults aged 18 to 55 years. Two studies (MTA02 and MTA12) were performed in healthy adolescents aged 11 to 18 years. Two studies (603-02 and MTA08) were performed in healthy children aged 2 to 10 years.

The immune responses to Menactra vaccine compared to Menomune vaccine in participants in the three age groups were non-inferior for all serogroups. Menactra vaccine tended to induce significantly higher levels of SBA compared to the Menomune vaccine. In adolescents and adults, the SBA antibody results were similar. In children, however, the comparative response pattern was slightly different than that observed for adolescents and adults. There were observable variations in the immune response profile of participants in each age group. The magnitude of the antibody response in children, as measured by GMT, was lower than that measured in adults and adolescents. This result was expected based on the

relative maturity of the immune system in each of these age groups. In each age group, the percentages of participants with ≥ 4-fold rise in SBA-BR for each serogroup were comparable across the studies. The levels of antibody achieved were beyond the levels needed for protection.

### Evaluator's Overall Conclusions on Clinical Efficacy

In terms of efficacy, the studies were designed to show non-inferiority in comparison to Menomune and do so. The only detectable immunogenicity result that did not satisfy the study objective in the efficacy studies was the lot consistency. Consistency in the response to C and Y was not shown at the high level of antibody. But this result is almost certainly not clinically relevant. Some good evidence of this vaccine being able to produce an immune memory was shown in Study MTA17. Increased avidity was found in conjugate primed individuals and it increased after challenge with low dose polysaccharide vaccine. Further evidence of immune memory was generated in Study MTA 19 where adolescents who had received a single dose of Menactra or Menomune 3 years earlier were boosted with a dose of Menactra vaccine and then compared to a vaccine naïve control group.

When Menactra vaccine was administered concomitantly with Td vaccine, the level of anti-diphtheria was 7 to 8 times higher than the expected level induced by the vaccines individually. The underlying mechanism for this observation is currently unknown, but the concomitant administration of Menactra vaccine with Td vaccine seems to be safe and well tolerated and the immune responses were not compromised. Anti-diphtheria immune responses were also measured in a subset of adolescent recipients in Study MTA02. In this study, Menactra vaccine was administered without concomitant vaccines, and the immune response was higher than seen with the Td vaccine alone but less than seen with concomitant administration of Td vaccine and Menactra vaccines. Similarly, in Study MTA11, the concomitant administration of Menactra vaccine with Typhim Vi vaccine was evaluated and no interference was found.

## Safety

### Introduction

The nine studies containing safety data in the current Australian submission and the parameters collected are shown in Table 29. The safety profile of all administered vaccines during this clinical development program was documented using five categories of adverse events (AEs):

1) Immediate reactions (within 30 minutes);

2) Solicited local reactions (Days 0 to7);

3) Solicited systemic reactions (Days 0 to7);

4) Unsolicited AEs

• Days 0 to 28,

• Day 29 to Month 6;

5) Serious adverse events (SAEs) (duration of study).

**Table 29: Safety Parameters Collected and Time Windows for Collection in Clinical Studies Included in the Summary of Clinical Safety**

| | | Adults | | | Adolescents | | | Children | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Safety Parameter | Time window for capture | MTA09 | MTA14 | MTA11 | MTA02 | MTA04 | MTA12 | 603-02 | MTA08 | MTA15 |
| Immediate Reactions | Day 0† + 30 mins. | X* | X | X | X | X | X | X | X | X |
| Solicited Local Reactions | Day 0 + 7 days | X | X | X | X | X | X | X | X | X |
| Solicited Systemic Reactions | Day 0 + 7 days | X | X | X | X | X | X | X | X | X |
| Unsolicited AEs | Day 0 to Day 28 | X | X | X | X | X | X | X | X | X |
| | Day 29 to Day 56 | NC‡ | NC | X§ | NC | NC | X§ | NC | NC | NC |
| | Day 29 to Month 6 | X | X | NC | X | X | NC | NC | X | NC |
| SAEs | Day 0 to end of participant's follow-up | X | X | X | X | X | X | X | X | X |

* Note .X. indicates that the parameter was documented in that particular study. Day 0 = Day of first trial vaccine administration (just after vaccination). NC = Not collected

**Immediate Reactions (Within 30 minutes)**

An immediate reaction was defined as any AE that started within 30 minutes of the vaccination. Immediate reactions were unsolicited. Both clinical severity and relatedness to the study vaccines of all immediate reactions were documented.

**Solicited Local Reactions (Day 0 to Day 7)**

A solicited local reaction was defined as any reaction corresponding to one of the vaccine injection site reactions listed on the pre-printed diary card given to the participants and which started on the evening of vaccination (Day 0) or up to Day 7 after vaccination. Any of the events on the diary card that started on or after Day 8 were reported and analyzed as unsolicited AEs. The solicited local reactions were:

• Redness;

• Swelling;

• Induration; and

• Pain at the injection site.

The clinical severity (mild, moderate, severe) of all solicited local reactions was collected.

**Solicited Systemic Reactions (Day 0 to Day 7)**

A solicited systemic reaction was defined as any reaction corresponding to one of the medical systemic conditions listed on the pre-printed diary card given to the participant and

which started on the evening of vaccination or up to Day 7 after vaccination. The solicited systemic reactions evaluated in each study are listed in Table 30.

**Table 30: Solicited Systemic Reactions Collected by Study**

| Systemic Reaction | Adults | | | Adolescents | | | Children | | |
|---|---|---|---|---|---|---|---|---|---|
| | MTA09 | MTA14 | MTA11 | MTA02 | MTA04 | MTA12 | 603-02 | MTA08 | MTA15 |
| Temperature | X | X | X | X | X | X | X | X | X |
| Anorexia | X | X | X | X | X | X | X | X | X |
| Vomiting | X | X | X | X | X | X | X | X | X |
| Diarrhea | X | X | X | X | X | X | X | X | X |
| Drowsiness | NS | NS | NS | NS | NS | NS | X | X | X |
| Irritability | NS | NS | NS | NS | NS | NS | X | X | X |
| Headache | X | X | X | X | X | X | NS | NS | NS |
| Rash | X | X | X | X | X | X | NS | X | X |
| Hives | NS | NS | NS | NS | NS | NS | X | NS | NS |
| Fatigue | X | X | X | X | X | X | NS | NS | NS |
| Chills | X | X | X | NS | X | X | NS | NS | NS |
| Arthralgia | X | X | X | NS | X | X | NS | X | NS |
| Malaise | X | X | X | NS | X | X | NS | NS | NS |
| Seizures | X | X | X | NS | X | X | NS | X | X |

Note: X indicates that the reaction was collected in that particular study. NS = Not solicited

### Unsolicited Adverse Events (Day 0 to Day 28)

An unsolicited AE was defined as any AE that started during Day 0 to Day 7 and did not correspond to one of the reactions listed on the pre-printed diary card, or any AE that started during Day 8 to Day 28 and was reported on the diary card or to study personnel. The clinical severity and relatedness to the study vaccines of all unsolicited AEs were assessed and documented by the investigators. For participants enrolled in Study MTA11 and MTA12 studies, there were two consecutive vaccination visits (one on Day 0 and one on Day 28). The follow-up period was 28 days after each study visit, so the total duration for the collection of unsolicited AEs was 56 days.

### Unsolicited Significant Adverse Events (Day 29 to Month 6)

Only significant unsolicited AEs were reported during the period between Day 29 and Month 6. Only five studies contributed to the documentation of this safety parameter (all these studies were comparative studies using the Menomune vaccine; Studies MTA09 and MTA14 in adults, Studies MTA02 and MTA04 in adolescents, and Study MTA08 in children). Significant AEs were defined as any new onset of a clinical sign, symptom, or laboratory abnormality discovered within the period between Day 29 and Month 6 following vaccination that prompted the participant to seek medical advice. Particular attention was given to newly diagnosed or new onset of seizure, idiopathic thrombocytopenia, autoimmune hemolytic anemia, bronchial asthma, insulin-dependent diabetes mellitus,

neutropenia and autoimmune disease not otherwise specified. The clinical severity and relatedness to the study vaccines of these were assessed by the investigators.

**Serious Adverse Events**

A SAE was defined as any AE occurring at any time during the study period that resulted in any of the following outcomes:

- death,
- a life-threatening adverse drug experience,
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant disability/incapacity,
- a congenital anomaly/birth defect.

The clinical severity and relatedness to the study vaccines of all SAEs were assessed by the investigators.

**Menactra Vaccine versus Menomune Vaccine Comparisons**

For all studies, the safety comparison objectives were defined as a comparison of the safety profile for Menactra vaccine and Menomune vaccine recipients. Safety endpoint was defined as the percentage of participants presenting at least one severe (graded 3 [severe] on a scale of 1 to 3) solicited systemic reaction between Day 0 and Day 7 (Studies MTA09, MTA04, MTA08, MTA14, and MTA02) or as the percentage of participants presenting with at least one fever episode ≥ 38.0°C (axillary) during Day 0 to Day 7 (Study 603-02). Severe solicited reactions were selected because they were considered the most clinically relevant following vaccine administration. All statistical hypotheses tested the non-inferiority of the Menactra vaccine when compared to the Menomune vaccine.

**Menactra Vaccine Lot Safety Comparison (Study MTA14)**

In Study MTA14, a similar definition was used for the safety comparison among the three Menactra vaccine consistency lots. Similarity was defined as the upper limit of the two-sided 95.0% CI of the difference in percentage of participants presenting with at least one severe solicited systemic reaction during Day 0 to Day 7 (most reactogenic Menactra vaccine lot minus least reactogenic Menactra vaccine lot) being less than 10 percentage points.

**Interference Studies**

No primary or secondary safety objectives were defined in Studies MTA11 and MTA12, where safety was an observational objective.

**Patient Exposure**

Menactra vaccine safety information was documented in:

- 3911 adults over 18 years of age;
- 3729 adolescents aged 11 to 18 years; and
- 2460 children aged 2 to 10 years.

Tables 31-33 shows the disposition of all age groups and the outcome in terms of completion, adverse events, follow up and compliance.

**Table 31: Summary of Participant Disposition in Adults.**

| | MTA09 | | MTA14 | | | | MTA11 | |
|---|---|---|---|---|---|---|---|---|
| | Menactra Vaccine n (%)* | Menomune Vaccine n (%)* | Menactra Vaccine Lot 1 n (%)* | Menactra Vaccine Lot 2 n (%)* | Menactra Vaccine Lot 3 n (%)* | Menomune Vaccine n (%)* | Group A† n (%)* | Group B‡ n (%)* |
| **Safety population** | 1384 (100.0) | 1170 (100.0) | 527 (100.0) | 528 (100.0) | 527 (100.0) | 458 (100.0) | 469 (100.0) | 476 (100.0) |
| **Completed Study** | | | | | | | | |
| Day 56 follow-up | - | - | - | - | - | - | 432 (92.1) | 439 (92.2) |
| Month 6 safety follow-up | 1301 (94.0) | 1099 (93.9) | 491 (93.2) | 480 (90.9) | 490 (93.0) | 425 (92.8) | - | - |
| **Did not complete Study** | 83 (6.0) | 71 (6.1) | 36 (6.8) | 48 (9.1) | 37 (7.0) | 33 (7.2) | 37 (7.9) | 37 (7.8) |
| **Reasons for withdrawal** | | | | | | | | |
| Adverse event | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.2) | 1 (0.2) | 0 (0.0) | 0 (0.0) |
| Lost to follow-up | 67 (4.8) | 52 (4.4) | 19 (3.6) | 34 (6.4) | 24 (4.6) | 19 (4.1) | 16 (3.4) | 8 (1.7) |
| Non-compliance | 13 (0.9) | 16 (1.4) | 14 (2.7) | 12 (2.3) | 11 (2.1) | 8 (1.7) | 14 (3.0) | 19 (4.0) |
| Voluntary withdrawal | 3 (0.2) | 2 (0.2) | 3 (0.6) | 2 (0.4) | 1 (0.2) | 5 (1.1) | 6 (1.3) | 10 (2.1) |
| Other | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.2) | 0 (0.0) |

* Percentages are based on the total number of randomized subjects enrolled in each treatment group. Group A: Received Typhim Vi vaccine + Menactra vaccine (Visit 1) then Placebo (Visit 2). Group B: Received Typhim Vi vaccine + Placebo (Visit 1) then Menactra vaccine (Visit 2).

**Table 32: Summary of Participant Disposition in Adolescents.**

| | MTA02 | | MTA04 | | MTA12 | |
|---|---|---|---|---|---|---|
| | Menactra Vaccine n (%)* | Menomune Vaccine n (%)* | Menactra Vaccine n (%)* | Menomune Vaccine n (%)* | Group A† n (%)* | Group B‡ n (%)* |
| **Safety population** | 440 (100.0) | 441 (100.0) | 2270 (100.0) | 972 (100.0) | 507 (100.0) | 512 (100.0) |
| **Completed Study** | | | | | | |
| Day 56 follow-up | - | - | - | - | 490 (96.6) | 498 (97.3) |
| Month 6 safety follow-up | 436 (99.1) | 435 (98.6) | 2250 (99.1) | 961 (98.9) | - | - |
| **Did not complete Study** | 4 (1.0) | 6 (1.4) | 20 (0.9) | 11 (1.1) | 17 (3.4) | 14 (2.7) |
| **Reasons for withdrawal** | | | | | | |
| Adverse event | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Lost to follow-up | 2 (0.5) | 4 (0.9) | 13 (0.6) | 7 (0.7) | 1 (0.2) | 1 (0.2) |
| Non-compliance | 0 (0.0) | 0 (0.0) | 2 (0.1) | 2 (0.2) | 7 (1.4) | 5 (1.0) |
| Voluntary withdrawal | 2 (0.5) | 2 (0.5) | 5 (0.2) | 1 (0.1) | 9 (1.8) | 7 (1.4) |
| Other | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.2) |

* Percentages are based on the total number of randomized subjects enrolled in each treatment group. Group A: Received Td vaccine + Menactra vaccine (Visit 1) then Placebo (Visit 2). Group B: Received Td vaccine + Placebo (Visit 1) then Menactra vaccine (Visit 2).

**Table 33: Summary of Participant Disposition in Children.**

| | 603-02 | | MTA08 | | | | | | MTA15 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Menactra Vaccine | | | Menomune Vaccine | | | | |
| | Menactra Vaccine | Menomune Vaccine | US | Chilean | All | US | Chilean | All | Menactra Vaccine | Menomune Vaccine |
| | n (%)* | n (%)* | n (%)* | n (%)* | n (%)* | n (%)* | n (%)* | n (%)* | n (%)* | n (%)* |
| **Safety population** | 696 (100.0) | 702 (100.0) | 1164 (100.0) | 548 (100.0) | 1712 (100.0) | 1031 (100.0) | 488 (100.0) | 1519 (100.0) | 52 (100.0) | 50 (100.0) |
| **Completed Study** | | | | | | | | | | |
| Day 28 follow up | - | - | - | - | - | - | - | - | 50 (96.2) | 47 (94.0) |
| Month 6 safety follow-up | 664 (95.4) | 670 (95.4) | 1148 (98.6) | 548 (100.0) | 1696 (99.1) | 1016 (98.5) | 488 (100.0) | 1504 (99.0) | - | - |
| **Did not complete Study** | 32 (4.6) | 32 (4.6) | 16 (1.4) | 0 (0.0) | 16 (0.9) | 15 (1.5) | 0 (0.0) | 15 (1.0) | 2 (3.8) | 3 (6.0) |
| **Reasons for withdrawal** | | | | | | | | | | |
| Adverse event | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Lost to follow-up | 7 (1.0) | 6 (0.9) | 16 (1.4) | 0 (0.0) | 16 (0.9) | 15 (1.5) | 0 (0.0) | 15 (1.0) | 1 (1.9) | 2 (4.0) |
| Non-compliance | 7 (1.0) | 3 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Voluntary withdrawal | 18 (2.6) | 21 (3.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (1.9) | 2 (2.0) |
| Other | 0 (0.0) | 2 (0.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

* Percentages are based on the total number of randomized subjects enrolled in each treatment group.

In the three studies in adults, there was a higher proportion of female participants compared to male participants (2:1), while female and male participants were more evenly distributed in the studies in children and adolescents. In addition, for the studies in children, it should be noted that the median age of participants was 3 years in Study 603-02 compared to 6 years in Study MTA08, although the recruitment age range was 2 to 10 years for both studies. Within Study MTA08, the median age of Chilean participants was 5 years compared to 6 years for US participants.

## Adverse Events

### *Common Adverse Events following Menactra Vaccine in Meningococcal Vaccine-Naïve Populations*

*Unsolicited Immediate Reactions after Vaccination*

Four adults out of 3412 (0.1%) who received Menactra vaccine presented six immediate reactions after vaccination, while three adults out of 1628 (0.2%) who received Menomune vaccine presented six immediate reactions after vaccination. Most of these reactions were considered to be mild and reversible. Eleven adolescents out of 3213 (0.3%) who received Menactra vaccine presented eighteen immediate reactions after vaccination, while three adolescents out of 1413 (0.2%) who received Menomune vaccine presented three immediate reactions after vaccination. Most of these reactions (13/18 in Menactra vaccine recipients and 3/3 in Menomune vaccine recipients) were considered to be mild and reversible. Five children out of 1860 (0.3%) who received Menactra vaccine presented five immediate reactions after vaccination, while seven children out of 1733 (0.4%) who received Menomune vaccine presented seven immediate reactions after vaccination. All these reactions were of mild severity and reversible.

*Solicited Local Reactions Day 0-Day 7 at the Meningococcal Vaccine Injection Site*

The following three tables present, by age group and for each study, the numbers and percentages of participants reporting at least one solicited local reaction and at least one

severe solicited local reaction within the 7 days following injection of either Menactra vaccine or Menomune vaccine.

**Table 34: Number and Percentage of Adults Participants Reporting at Least One Solicited Local Reaction and at Least One Severe Solicited Local Reaction During Days 0-7, by Reaction Type and Study (Safety Population)**

| | MTA09 | | | | MTA14 | | | | | | | | | | MTA11 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Menactra Vaccine | | Menomune Vaccine | | Menactra Vaccine Lot 1 | | Menactra Vaccine Lot 2 | | Menactra Vaccine Lot 3 | | Menactra Vaccine* (26-55 years) | | Menomune Vaccine (26-55 years) | | Group A† | | Group B‡ | |
| | n/N | % | n/N | % | n/N | % | n/N | % | n/N | % | n/N | % | n/N | % | n/N | % | n/N | % |
| ≥ 1 Reaction | 790/1371 | 57.6 | 644/1159 | 55.6 | 285/521 | 54.7 | 278/521 | 53.4 | 296/522 | 56.7 | 290/685 | 42.3 | 118/454 | 26.0 | 234/456 | 51.3 | 207/439 | 47.2 |
| Severe§ | 23/1371 | 1.7 | 2/1159 | 0.2 | 5/521 | 1.0 | 4/521 | 0.8 | 7/522 | 1.3 | 6/685 | 0.9 | 0/454 | 0.0 | 9/456 | 2.0 | 12/439 | 2.7 |
| Redness | 198/1371 | 14.4 | 185/1159 | 16.0 | 60/521 | 11.5 | 75/521 | 14.4 | 63/522 | 12.1 | 72/685 | 10.5 | 45/454 | 9.9 | 52/456 | 11.4 | 62/439 | 14.1 |
| Severe§ | 15/1371 | 1.1 | 1/1159 | 0.1 | 4/521 | 0.8 | 2/521 | 0.4 | 3/522 | 0.6 | 4/685 | 0.6 | 0/454 | 0.0 | 4/456 | 0.9 | 3/439 | 0.7 |
| Swelling | 173/1371 | 12.6 | 88/1159 | 7.6 | 58/521 | 11.1 | 55/521 | 10.6 | 56/522 | 10.7 | 73/685 | 10.7 | 21/454 | 4.6 | 61/456 | 13.4 | 50/439 | 11.4 |
| Severe§ | 13/1371 | 0.9 | 0/1159 | 0.0 | 2/521 | 0.4 | 2/521 | 0.4 | 4/522 | 0.8 | 3/685 | 0.4 | 0/454 | 0.0 | 3/456 | 0.7 | 4/439 | 0.9 |
| Induration | 235/1371 | 17.1 | 127/1159 | 11.0 | 75/521 | 14.4 | 90/521 | 17.3 | 92/522 | 17.6 | 92/685 | 13.4 | 25/454 | 5.5 | 78/456 | 17.1 | 67/439 | 15.3 |
| Severe§ | 9/1371 | 0.7 | 0/1159 | 0.0 | 2/521 | 0.4 | 1/521 | 0.2 | 4/522 | 0.8 | 4/685 | 0.6 | 0/454 | 0.0 | 3/456 | 0.7 | 3/439 | 0.7 |
| Pain | 739/1371 | 53.9 | 558/1159 | 48.1 | 264/521 | 50.7 | 254/521 | 48.8 | 275/522 | 52.7 | 264/685 | 38.5 | 90/454 | 19.8 | 212/456 | 46.5 | 192/439 | 43.7 |
| Severe§ | 3/1371 | 0.2 | 1/1159 | 0.1 | 0/521 | 0.0 | 1/521 | 0.2 | 1/522 | 0.2 | 0/685 | 0.0 | 0/454 | 0.0 | 3/456 | 0.7 | 8/439 | 1.8 |

* Group A: Menactra vaccine injection site at Visit 1 (subjects received Typhim Vi vaccine + Menactra vaccine [Visit 1] then Placebo [Visit 2]). Group B: Menactra vaccine injection site at Visit 2 (subjects received Typhim Vi vaccine + Placebo [Visit 1] then Menactra vaccine [Visit 2]).

**Table 35: Number and Percentage of Adolescent Participants Reporting at Least One Solicited Local Reaction and at Least One Severe Solicited Local Reaction During Days 0-7, by Reaction Type and Study (Safety Population)**

| | MTA02 | | | | MTA04 | | | | MTA12 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Menactra Vaccine | | Menomune Vaccine | | Menactra Vaccine | | Menomune Vaccine | | Group A* | | Group B† | |
| | n/N | % | n/N | % | n/N | % | n/N | % | n/N | % | n/N | % |
| ≥ 1 Reaction | 317/438 | 72.4 | 153/441 | 34.7 | 1420/2264 | 62.7 | 310/970 | 32.0 | 293/505 | 58.0 | 288/505 | 57.0 |
| Severe‡ | 5/438 | 1.1 | 0/441 | 0.0 | 26/2264 | 1.1 | 0/970 | 0.0 | 11/505 | 2.2 | 11/505 | 2.2 |
| Redness | 53/438 | 12.1 | 28/441 | 6.3 | 247/2264 | 10.9 | 55/970 | 5.7 | 61/505 | 12.1 | 56/505 | 11.1 |
| Severe‡ | 1/438 | 0.2 | 0/441 | 0.0 | 13/2264 | 0.6 | 0/970 | 0.0 | 6/505 | 1.2 | 5/505 | 1.0 |
| Swelling | 63/438 | 14.4 | 24/441 | 5.4 | 245/2264 | 10.8 | 35/970 | 3.6 | 59/505 | 11.7 | 66/505 | 13.1 |
| Severe‡ | 3/438 | 0.7 | 0/441 | 0.0 | 11/2264 | 0.5 | 0/970 | 0.0 | 3/505 | 0.6 | 7/505 | 1.4 |
| Induration | 89/438 | 20.3 | 34/441 | 7.7 | 355/2264 | 15.7 | 50/970 | 5.2 | 86/505 | 17.0 | 78/505 | 15.4 |
| Severe‡ | 3/438 | 0.7 | 0/441 | 0.0 | 7/2264 | 0.3 | 0/970 | 0.0 | 5/505 | 1.0 | 5/505 | 1.0 |
| Pain | 302/438 | 68.9 | 133/441 | 30.2 | 1340/2264 | 59.2 | 278/970 | 28.7 | 267/505 | 52.9 | 270/505 | 53.5 |
| Severe‡ | 1/438 | 0.2 | 0/441 | 0.0 | 6/2264 | 0.3 | 0/970 | 0.0 | 0/505 | 0.0 | 4/505 | 0.8 |

* Group A: Menactra vaccine injection site at Visit 1 (subjects received Td vaccine + Menactra vaccine [Visit 1] then Placebo [Visit 2]). . Group B: Menactra vaccine injection site at Visit 2 (subjects received Td vaccine + Placebo [Visit 1] then Menactra vaccine [Visit 2]).

**Table 36: Number and Percentage of Children Participants Reporting at Least One Solicited Local Reaction and at Least One Severe Solicited Local Reaction During Days 0-7, by Reaction Type and Study (Safety Population) 603-02 MTA08**

| | 603-02 | | | | MTA08 | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Menactra Vaccine | | Menomune Vaccine | | Menactra Vaccine | | | | | | Menomune Vaccine | | | | | |
| | | | | | US | | Chilean | | All | | US | | Chilean | | All | |
| | n/N | % | n/N | % | n/N | % | n/N | % | n/N | % | n/N | % | n/N | % | n/N | % |
| ≥ 1 Reaction | 407/692 | 58.8 | 408/700 | 58.3 | 613/1156 | 53.0 | 188/548 | 34.3 | 801/1704 | 47.0 | 321/1027 | 31.3 | 220/488 | 45.1 | 541/1515 | 35.7 |
| Severe* | 35/692 | 5.1 | 5/700 | 0.7 | 49/1156 | 4.2 | 2/548 | 0.4 | 51/1704 | 3.0 | 0/1027 | 0.0 | 0/488 | 0.0 | 0/1515 | 0.0 |
| Redness | 204/692 | 29.5 | 213/700 | 30.4 | 252/1156 | 21.8 | 53/548 | 9.7 | 305/1704 | 17.9 | 81/1027 | 7.9 | 61/488 | 12.5 | 142/1515 | 9.4 |
| Severe* | 30/692 | 4.3 | 3/700 | 0.4 | 45/1156 | 3.9 | 2/548 | 0.4 | 47/1704 | 2.8 | 0/1027 | 0.0 | 0/488 | 0.0 | 0/1515 | 0.0 |
| Swelling | 142/692 | 20.5 | 102/700 | 14.6 | 201/1156 | 17.4 | 42/548 | 7.7 | 243/1704 | 14.3 | 29/1027 | 2.8 | 45/488 | 9.2 | 74/1515 | 4.9 |
| Severe* | 8/692 | 1.2 | 2/700 | 0.3 | 22/1156 | 1.9 | 0/548 | 0.0 | 22/1704 | 1.3 | 0/1027 | 0.0 | 0/488 | 0.0 | 0/1515 | 0.0 |
| Induration | 153/692 | 22.1 | 109/700 | 15.6 | 219/1156 | 18.9 | 56/548 | 10.2 | 275/1704 | 16.1 | 43/1027 | 4.2 | 36/488 | 7.4 | 79/1515 | 5.2 |
| Severe* | 7/692 | 1.0 | 1/700 | 0.1 | 16/1156 | 1.4 | 0/548 | 0.0 | 16/1704 | 0.9 | 0/1027 | 0.0 | 0/488 | 0.0 | 0/1515 | 0.0 |
| Pain | 333/692 | 48.1 | 328/700 | 46.9 | 520/1156 | 45.0 | 156/548 | 28.5 | 676/1704 | 39.7 | 268/1027 | 26.1 | 193/488 | 39.5 | 461/1515 | 30.4 |
| Severe* | 5/692 | 0.7 | 2/700 | 0.3 | 3/1156 | 0.3 | 0/548 | 0.0 | 3/1704 | 0.2 | 0/1027 | 0.0 | 0/488 | 0.0 | 0/1515 | 0.0 |

In adults, 47.2% to 57.6% of participants (depending on study) reported at least one solicited local reaction at the Menactra vaccine injection site. Pain at the injection site was the most frequently reported reaction, followed by induration, redness and swelling. At least one severe solicited local reaction was reported in 0.8% to 2.7% of participants after having received Menactra vaccine. Redness at the injection site was the most frequently reported severe solicited local reaction. In adolescents, 57.0% to 72.4% of the participants reported at least one solicited local reaction at the Menactra vaccine injection site. Pain at the injection site was the most frequently reported reaction, followed by induration, and redness or swelling. At least one severe solicited local reaction was reported in 1.1% to 2.2% of participants reported after having received Menactra vaccine. Redness, swelling and induration at the injection site were the most frequently reported severe solicited local reactions. In children, 47.0% to 58.8% of participants (depending on study) reported at least one solicited local reaction. Pain at the injection site was the most frequently reported reaction, followed by redness or induration, and swelling. At least one severe solicited local reaction was reported in 3.0% to 5.1% of participants after having received Menactra vaccine. Redness at the injection site was the most frequently reported severe solicited local reaction. When considering only the comparative studies (MTA09 and MTA14 in adults, MTA02 and MTA04 in adolescents and 603-02 and MTA08 in children), solicited local reactions were more frequently reported in Menactra vaccine recipients than in Menomune vaccine recipients. When considering only the severe solicited local reactions reported in the comparative studies, only 0% to 0.7% of Menomune vaccine recipients reported such events compared to 0.8% to 5.1% of Menactra vaccine recipients.

*Solicited Systemic Reactions Day 0 to Day 7 after Vaccination*

The following three tables present by age group and for each study, the numbers and percentages of participants reporting at least one solicited systemic reaction and at least one severe solicited systemic reaction within 7 days of the injection of either the Menactra vaccine or the Menomune vaccine.

**Table 37: Number and Percentage of Adults Participants Reporting at Least One Solicited Systemic Reaction and at Least One Severe Solicited Systemic Reaction During Days 0-7, by Reaction Type and Study (Safety Population)**

| | MTA09 | | | | MTA14 | | | | | | | | | | MTA11 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Menactra Vaccine | | Menomune Vaccine | | Menactra Vaccine Lot 1 | | Menactra Vaccine Lot 2 | | Menactra Vaccine Lot 3 | | Menactra Vaccine* (26-55 years) | | Menomune Vaccine (26-55 years) | | Group A† | | Group B‡ | |
| | n/N | % | n/N | % | n/N | % | n/N | % | n/N | % | n/N | % | n/N | % | n/N | % | n/N | % |
| ≥ 1 Reaction | 849/1371 | 61.9 | 699/1159 | 60.3 | 311/521 | 59.7 | 310/521 | 59.5 | 320/522 | 61.3 | 366/685 | 53.4 | 224/455 | 49.2 | 276/456 | 60.5 | 211/439 | 48.1 |
| Severe§ | 52/1371 | 3.8 | 30/1159 | 2.6 | 18/521 | 3.5 | 17/521 | 3.3 | 14/522 | 2.7 | 15/685 | 2.2 | 25/455 | 5.5 | 24/456 | 5.3 | 10/439 | 2.3 |
| Fever | 21/1371 | 1.5 | 6/1159 | 0.5 | 4/515 | 0.8 | 7/516 | 1.4 | 3/516 | 0.6 | 4/683 | 0.6 | 2/453 | 0.4 | 4/448 | 0.9 | 5/434 | 1.2 |
| Severe§ | 0/1371 | 0.0 | 0/1159 | 0.0 | 0/515 | 0.0 | 0/516 | 0.0 | 1/516 | 0.2 | 0/683 | 0.0 | 0/453 | 0.0 | 0/448 | 0.0 | 0/434 | 0.0 |
| Chills | 133/1371 | 9.7 | 65/1159 | 5.6 | 36/521 | 6.9 | 30/521 | 5.8 | 48/522 | 9.2 | 45/685 | 6.6 | 15/454 | 3.3 | 30/455 | 6.6 | 35/439 | 8.0 |
| Severe§ | 8/1371 | 0.6 | 0/1159 | 0.0 | 1/521 | 0.2 | 1/521 | 0.2 | 0/522 | 0.0 | 0/685 | 0.0 | 2/454 | 0.4 | 2/455 | 0.4 | 2/439 | 0.5 |
| Anorexia | 162/1371 | 11.8 | 115/1159 | 9.9 | 53/521 | 10.2 | 61/521 | 11.7 | 65/522 | 12.5 | 64/685 | 9.3 | 35/454 | 7.7 | 50/456 | 11.0 | 38/439 | 8.7 |
| Severe§ | 5/1371 | 0.4 | 5/1159 | 0.4 | 1/521 | 0.2 | 3/521 | 0.6 | 0/522 | 0.0 | 1/685 | 0.1 | 1/454 | 0.2 | 3/456 | 0.7 | 2/439 | 0.5 |
| Vomiting | 32/1371 | 2.3 | 17/1159 | 1.5 | 12/521 | 2.3 | 11/521 | 2.1 | 4/522 | 0.8 | 8/685 | 1.2 | 6/455 | 1.3 | 10/456 | 2.2 | 8/439 | 1.8 |
| Severe§ | 3/1371 | 0.2 | 5/1159 | 0.4 | 1/521 | 0.2 | 0/521 | 0.0 | 0/522 | 0.0 | 0/685 | 0.0 | 0/455 | 0.0 | 2/456 | 0.4 | 1/439 | 0.2 |
| Diarrhea | 219/1371 | 16.0 | 162/1159 | 14.0 | 91/521 | 17.5 | 81/521 | 15.5 | 95/522 | 18.2 | 105/685 | 15.3 | 70/455 | 15.4 | 54/455 | 11.9 | 32/439 | 7.3 |
| Severe§ | 5/1371 | 0.4 | 4/1159 | 0.3 | 3/521 | 0.6 | 2/521 | 0.4 | 3/522 | 0.6 | 2/685 | 0.3 | 3/455 | 0.7 | 1/455 | 0.2 | 0/439 | 0.0 |
| Arthralgia | 272/1371 | 19.8 | 185/1159 | 16.0 | 103/521 | 19.8 | 93/521 | 17.9 | 103/522 | 19.7 | 104/685 | 15.2 | 57/455 | 12.5 | 84/455 | 18.5 | 51/439 | 11.6 |
| Severe§ | 4/1371 | 0.3 | 1/1159 | 0.1 | 3/521 | 0.6 | 4/521 | 0.8 | 0/522 | 0.0 | 0/685 | 0.0 | 2/455 | 0.4 | 3/455 | 0.7 | 2/439 | 0.5 |
| Headache | 568/1371 | 41.4 | 484/1159 | 41.8 | 219/521 | 42.0 | 198/521 | 38.0 | 209/522 | 40.0 | 240/685 | 35.0 | 153/455 | 33.6 | 185/456 | 40.6 | 143/439 | 32.6 |
| Severe§ | 16/1371 | 1.2 | 11/1159 | 0.9 | 3/521 | 0.6 | 3/521 | 0.6 | 2/522 | 0.4 | 3/685 | 0.4 | 5/455 | 1.1 | 6/456 | 1.3 | 2/439 | 0.5 |
| Fatigue | 476/1371 | 34.7 | 374/1159 | 32.3 | 168/521 | 32.2 | 172/521 | 33.0 | 183/522 | 35.1 | 192/685 | 28.0 | 114/455 | 25.1 | 172/456 | 37.7 | 119/439 | 27.1 |
| Severe§ | 12/1371 | 0.9 | 5/1159 | 0.4 | 4/521 | 0.8 | 3/521 | 0.6 | 3/522 | 0.6 | 4/685 | 0.6 | 6/455 | 1.3 | 8/456 | 1.8 | 4/439 | 0.9 |

| | MTA09 | | | | MTA14 | | | | | | | | | | MTA11 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Menactra Vaccine | | Menomune Vaccine | | Menactra Vaccine Lot 1 | | Menactra Vaccine Lot 2 | | Menactra Vaccine Lot 3 | | Menactra Vaccine* (26-55 years) | | Menomune Vaccine (26-55 years)* | | Group A** | | Group B† | |
| | n/N | % | n/N | % | n/N | % | n/N | % | n/N | % | n/N | % | n/N | % | n/N | % | n/N | % |
| Malaise | 324/1371 | 23.6 | 259/1159 | 22.3 | 116/521 | 22.3 | 110/521 | 21.1 | 123/522 | 23.6 | 134/685 | 19.6 | 80/455 | 17.6 | 106/455 | 23.3 | 87/439 | 19.8 |
| Severe§ | 15/1371 | 1.1 | 10/1159 | 0.9 | 5/521 | 1.0 | 3/521 | 0.6 | 0/522 | 0.0 | 2/685 | 0.3 | 8/455 | 1.8 | 6/455 | 1.3 | 7/439 | 1.6 |
| Rash | 19/1371 | 1.4 | 9/1159 | 0.8 | 8/521 | 1.5 | 7/521 | 1.3 | 7/522 | 1.3 | 7/685 | 1.0 | 11/454 | 2.4 | 11/455 | 2.4 | 2/439 | 0.5 |
| Seizures | 0/1371 | 0.0 | 0/1159 | 0.0 | 0/521 | 0.0 | 0/521 | 0.0 | 0/522 | 0.0 | 0/685 | 0.0 | 0/454 | 0.0 | 0/455 | 0.0 | 0/439 | 0.0 |

* Participants enrolled in the Menomune vaccine arm were older than participants of the Menactra vaccine arms. Therefore, for the Menactra vaccine (Total) column, only the subjects aged 26 to 55 years have been considered in this pool, in order to present their data comparatively to the Menomune vaccine enrolled subjects aged 26 to 55 years. **.** Group A: safety after Visit 1 (subjects received Typhim Vi vaccine + Menactra vaccine [Visit 1] then Placebo [Visit 2]). **.** Group B: safety after Visit 2 (subjects received Typhim Vi vaccine + Placebo [Visit 1] then Menactra vaccine [Visit 2]).

**Table 38: Number and Percentage of Adolescent Participants Reporting at Least One Solicited Systemic Reaction and at Least One Severe Solicited Systemic Reaction During Days 0-7, by Reaction Type and Study (Safety Population)**

| | MTA02 | | | | MTA04 | | | | MTA12 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Menactra Vaccine | | Menomune Vaccine | | Menactra Vaccine | | Menomune Vaccine | | Group A* | | Group B† | |
| | n/N | % | n/N | % | n/N | % | n/N | % | n/N | % | n/N | % |
| ≥ 1 Reaction | 251/439 | 57.2 | 229/441 | 51.9 | 1247/2265 | 55.1 | 472/970 | 48.7 | 296/505 | 58.6 | 181/505 | 35.8 |
| Severe‡ | 17/439 | 3.9 | 18/441 | 4.1 | 97/2265 | 4.3 | 25/970 | 2.6 | 24/505 | 4.8 | 16/505 | 3.2 |
| Fever | 15/439 | 3.4 | 11/440 | 2.5 | 115/2265 | 5.1 | 29/970 | 3.0 | 25/503 | 5.0 | 11/505 | 2.2 |
| Severe‡ | 1/439 | 0.2 | 0/440 | 0.0 | 0/2265 | 0.0 | 1/970 | 0.1 | 1/503 | 0.2 | 0/505 | 0.0 |
| Chills | - | - | - | - | 158/2265 | 7.0 | 34/970 | 3.5 | 56/505 | 11.1 | 18/505 | 3.6 |
| Severe‡ | - | - | - | - | 5/2265 | 0.2 | 1/970 | 0.1 | 3/505 | 0.6 | 0/505 | 0.0 |
| Anorexia | 54/439 | 12.3 | 54/441 | 12.2 | 243/2265 | 10.7 | 75/970 | 7.7 | 64/505 | 12.7 | 22/505 | 4.4 |
| Severe‡ | 4/439 | 0.9 | 3/441 | 0.7 | 7/2265 | 0.3 | 2/970 | 0.2 | 5/505 | 1.0 | 2/505 | 0.4 |
| Vomiting | 10/439 | 2.3 | 9/441 | 2.0 | 44/2265 | 1.9 | 14/970 | 1.4 | 23/505 | 4.6 | 7/505 | 1.4 |
| Severe‡ | 1/439 | 0.2 | 1/441 | 0.2 | 6/2265 | 0.3 | 3/970 | 0.3 | 0/505 | 0.0 | 1/505 | 0.2 |
| Diarrhea | 48/439 | 10.9 | 62/441 | 14.1 | 271/2265 | 12.0 | 99/970 | 10.2 | 45/505 | 8.9 | 19/505 | 3.8 |
| Severe‡ | 0/439 | 0.0 | 1/441 | 0.2 | 7/2265 | 0.3 | 0/970 | 0.0 | 1/505 | 0.2 | 0/505 | 0.0 |
| Arthralgia | - | - | - | - | 394/2265 | 17.4 | 99/970 | 10.2 | 127/505 | 25.1 | 61/505 | 12.1 |
| Severe‡ | - | - | - | - | 8/2265 | 0.4 | 1/970 | 0.1 | 4/505 | 0.8 | 1/505 | 0.2 |
| Headache | 197/439 | 44.9 | 174/441 | 39.5 | 807/2265 | 35.6 | 284/970 | 29.3 | 180/505 | 35.6 | 110/505 | 21.8 |
| Severe‡ | 7/439 | 1.6 | 8/441 | 1.8 | 24/2265 | 1.1 | 4/970 | 0.4 | 10/505 | 2.0 | 3/505 | 0.6 |
| Fatigue | 124/439 | 28.2 | 104/441 | 23.6 | 679/2265 | 30.0 | 243/970 | 25.1 | 161/505 | 31.9 | 85/505 | 16.8 |
| Severe‡ | 5/439 | 1.1 | 3/441 | 0.7 | 26/2265 | 1.1 | 2/970 | 0.2 | 7/505 | 1.4 | 5/505 | 1.0 |
| Malaise | - | - | - | - | 496/2265 | 21.9 | 163/970 | 16.8 | 119/505 | 23.6 | 61/505 | 12.1 |
| Severe‡ | - | - | - | - | 25/2265 | 1.1 | 4/970 | 0.4 | 11/505 | 2.2 | 5/505 | 1.0 |
| Rash | 7/439 | 1.6 | 7/441 | 1.6 | 37/2265 | 1.6 | 14/970 | 1.4 | 9/505 | 1.8 | 7/505 | 1.4 |
| Seizures | - | - | - | - | 0/2265 | 0.0 | 0/970 | 0.0 | 0/505 | 0.0 | 0/505 | 0.0 |

* Group A: safety after Visit 1 (subjects received Td vaccine + Menactra vaccine [Visit 1] then Placebo [Visit 2]). . Group B: safety after Visit 2 (subjects received Td vaccine + Placebo [Visit 1] then Menactra vaccine [Visit 2]).

**Table 39: Number and Percentage of Children Participants Reporting at Least One Solicited Systemic Reaction and at Least One Severe Solicited Systemic Reaction During Days 0-7, by Reaction Type and Study (Safety Population)**

| | 603-02 | | | | MTA08 | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Menactra Vaccine | | Menomune Vaccine | | Menactra Vaccine | | | | | | Menomune Vaccine | | | | | |
| | | | | | US | | Chilean | | All | | US | | Chilean | | All | |
| | n/N | % | n/N | % | n/N | % | n/N | % | n/N | % | n/N | % | n/N | % | n/N | % |
| ≥ 1 Reaction | 371/693 | 53.5 | 364/700 | 52.0 | 379/1157 | 32.8 | 198/548 | 36.1 | 577/1705 | 33.8 | 334/1027 | 32.5 | 180/488 | 36.9 | 514/1515 | 33.9 |
| Severe* | 53/693 | 7.6 | 25/700 | 3.6 | 54/1157 | 4.7 | 33/548 | 6.0 | 87/1705 | 5.1 | 49/1027 | 4.8 | 27/488 | 5.5 | 76/1515 | 5.0 |
| Fever | 77/674 | 11.4 | 82/684 | 12.0 | 60/1154 | 5.2 | 39/536 | 7.3 | 99/1690 | 5.9 | 53/1019 | 5.2 | 36/473 | 7.6 | 89/1492 | 6.0 |
| Severe* | 6/674 | 0.9 | 4/684 | 0.6 | 3/1154 | 0.3 | 0/536 | 0.0 | 3/1690 | 0.2 | 2/1019 | 0.2 | 2/473 | 0.4 | 4/1492 | 0.3 |
| Irritability | 244/693 | 35.2 | 211/700 | 30.1 | 143/1157 | 12.4 | 44/548 | 8.0 | 187/1705 | 11.0 | 125/1027 | 12.2 | 58/488 | 11.9 | 183/1515 | 12.1 |
| Severe* | 19/693 | 2.7 | 6/700 | 0.9 | 4/1157 | 0.3 | 0/548 | 0.0 | 4/1705 | 0.2 | 6/1027 | 0.6 | 0/488 | 0.0 | 6/1515 | 0.4 |
| Drowsiness | 180/693 | 26.0 | 169/700 | 24.1 | 125/1157 | 10.8 | 52/548 | 9.5 | 177/1705 | 10.4 | 115/1027 | 11.2 | 50/488 | 10.2 | 165/1515 | 10.9 |
| Severe* | 11/693 | 1.6 | 8/700 | 1.1 | 4/1157 | 0.3 | 0/548 | 0.0 | 4/1705 | 0.2 | 5/1027 | 0.5 | 0/488 | 0.0 | 5/1515 | 0.3 |
| Anorexia | 157/693 | 22.7 | 142/700 | 20.3 | 95/1157 | 8.2 | 47/548 | 8.6 | 142/1705 | 8.3 | 89/1027 | 8.7 | 50/488 | 10.2 | 139/1515 | 9.2 |
| Severe* | 12/693 | 1.7 | 3/700 | 0.4 | 5/1157 | 0.4 | 0/548 | 0.0 | 5/1705 | 0.3 | 8/1027 | 0.8 | 2/488 | 0.4 | 10/1515 | 0.7 |
| Vomiting | 41/693 | 5.9 | 49/700 | 7.0 | 35/1157 | 3.0 | 24/548 | 4.4 | 59/1705 | 3.5 | 28/1027 | 2.7 | 19/488 | 3.9 | 47/1515 | 3.1 |
| Severe* | 5/693 | 0.7 | 8/700 | 1.1 | 3/1157 | 0.3 | 1/548 | 0.2 | 4/1705 | 0.2 | 6/1027 | 0.6 | 0/488 | 0.0 | 6/1515 | 0.4 |
| Diarrhea | 110/693 | 15.9 | 110/700 | 15.7 | 129/1157 | 11.1 | 78/548 | 14.2 | 207/1705 | 12.1 | 121/1027 | 11.8 | 76/488 | 15.6 | 197/1515 | 13.0 |
| Severe* | 11/693 | 1.6 | 3/700 | 0.4 | 2/1157 | 0.2 | 2/548 | 0.4 | 4/1705 | 0.2 | 3/1027 | 0.3 | 2/488 | 0.4 | 5/1515 | 0.3 |
| Arthralgia | - | - | - | - | 79/1157 | 6.8 | 45/548 | 8.2 | 124/1705 | 7.3 | 54/1027 | 5.3 | 61/488 | 12.5 | 115/1515 | 7.6 |
| Severe* | - | - | - | - | 2/1157 | 0.2 | 0/548 | 0.0 | 2/1705 | 0.1 | 0/1027 | 0.0 | 0/488 | 0.0 | 0/1515 | 0.0 |
| Hives | 8/693 | 1.2 | 3/700 | 0.4 | - | - | - | - | - | - | - | - | - | - | - | - |
| Rash | - | - | - | - | 39/1157 | 3.4 | 31/548 | 5.7 | 70/1705 | 4.1 | 31/1027 | 3.0 | 22/488 | 4.5 | 53/1515 | 3.5 |
| Seizures | - | - | - | - | 0/1157 | 0.0 | 0/548 | 0.0 | 0/1705 | 0.0 | 0/1027 | 0.0 | 0/488 | 0.0 | 0/1515 | 0.0 |

In adults (Table 37), 48.1% to 61.9% of participants (depending on study) reported at least one solicited systemic reaction after receiving Menactra vaccine. Headache was the most frequently reported reaction, followed by fatigue, malaise, arthralgia and diarrhoea. Fever (of any severity) was reported by 0.6% to 1.5% of participants. Severe solicited systemic reactions were reported in 2.3% to 5.3% of participants after having received the Menactra vaccine. Severe fever was reported by 0% to 0.2% of the study participants. In adolescents (Table 38), 35.8% to 58.6% of participants reported at least one solicited systemic reaction after receiving Menactra vaccine. Similar to adults, headache was the most frequently

reported reaction in adolescents, followed by fatigue, malaise, arthralgia and diarrhoea. Severe solicited systemic reactions were reported in 3.2% to 4.8% of adolescents after receiving Menactra vaccine. Severe fever was reported by 0% to 0.2% of study participants. In children (Table 39), 33.8% to 53.5% of participants reported at least one solicited systemic reaction. Irritability, diarrhoea, drowsiness and anorexia were the most frequently reported reactions. Severe solicited systemic reactions were reported in 5.1% to 7.6% of participants after receiving Menactra vaccine. Severe fever was reported by 0.2% to 0.9% of study participants. When considering only the comparative studies (MTA09 and MTA14 in adults, MTA02 and MTA04 in adolescents, 603-02 and MTA08 in children), solicited systemic reactions were reported slightly more frequently in Menactra vaccine recipients than in Menomune vaccine recipients. The only exception was observed in the Chilean subjects in Study MTA08, where the safety profile was similar in the two study groups. Severe solicited systemic reactions were reported in 2.2% to 5.5% of Menomune vaccine recipients compared to 2.2% to 7.6% of Menactra vaccine recipients.

*Unsolicited Adverse Events during the Day 0 to Day 28 Period after Vaccination*

Out of 3339 adult participants who received Menactra vaccine, 930 (27.9%) presented 1323 unsolicited AEs during the period Day 0 to Day 28 after vaccination, while 461 participants out of 1593 who received Menomune vaccine (28.9%) presented 699 unsolicited AEs during Day 0 to Day 28 after vaccination. Respiratory, thoracic and mediastinal disorders, Infections and infestations, Musculoskeletal and connective tissue disorders, Gastrointestinal disorders and Reproductive system and breast disorders accounted for the majority of events reported. Only 1.1% and 1.5% of the Menactra vaccine and the Menomune vaccine recipients, respectively, reported at least one severe unsolicited AE between Days 0 and 28 after vaccination (Table 40).

**Table 40: Number (and %) of Participants Reporting Unsolicited AEs Starting Between Days 0 and 28 After Meningococcal Vaccination by System Organ Class (SOC), Vaccination Group and Severity and Number (and %) of These AEs by SOC, Vaccination Group and Severity (Safety Population) Adult Population (MTA09, MTA14, and Group B in MTA11)**

| | TetraMenD | | | Menomune | | |
|---|---|---|---|---|---|---|
| | Participants N[1]=3339 | | Events M[2]=1323 | Participants N[1]=1593 | | Events M[2]=699 |
| | Mild | Moderate | Severe | Mild | Moderate | Severe |
| System Organ Class | n (%)[3] | n (%)[3] | n (%)[3] | n (%)[3] | n (%)[3] | n (%)[3] |
| Any Reactions | | | | | | |
| Participants | 616( 18.4) | 277( 8.3) | 36( 1.1) | 321( 20.2) | 116( 7.3) | 24( 1.5) |
| Events | 929( 70.2) | 347( 26.2) | 45( 3.4) | 506( 72.4) | 167( 23.9) | 26( 3.7) |
| Respiratory, thoracic and mediastinal disorders | | | | | | |
| Participants | 172( 5.2) | 39( 1.2) | 4( 0.1) | 90( 5.6) | 19( 1.2) | 2( 0.1) |
| Events | 227( 17.2) | 48( 3.6) | 4( 0.3) | 117( 16.7) | 27( 3.9) | 2( 0.3) |
| Infections and infestations | | | | | | |
| Participants | 148( 4.4) | 86( 2.6) | 5( 0.1) | 100( 6.3) | 46( 2.9) | 5( 0.3) |
| Events | 160( 12.1) | 90( 6.8) | 7( 0.5) | 106( 15.2) | 51( 7.3) | 5( 0.7) |
| Musculoskeletal and connective tissue disorders | | | | | | |
| Participants | 132( 4.0) | 46( 1.4) | 5( 0.1) | 62( 3.9) | 15( 0.9) | 1( 0.1) |
| Events | 152( 11.5) | 52( 3.9) | 8( 0.6) | 71( 10.2) | 20( 2.9) | 1( 0.1) |
| Gastrointestinal disorders | | | | | | |
| Participants | 88( 2.6) | 29( 0.9) | 4( 0.1) | 48( 3.0) | 17( 1.1) | 4( 0.3) |
| Events | 94( 7.1) | 30( 2.3) | 4( 0.3) | 61( 8.7) | 21( 3.0) | 5( 0.7) |

[1] N: Number of participants in each treatment group with safety information for this time period. [2] M: Number of events in each treatment group. [3] n: Number of participants and % (n/N) reporting at least one event corresponding to a given SOC in each treatment group and number of events and % (n/M) reported in the given SOC.

The most frequently reported severe unsolicited AEs were from the Infections and infestations, Musculoskeletal and connective tissue disorders, Gastrointestinal disorders, and Injury, poisoning and procedural complications. Five participants who received Menactra vaccine (0.1%) experienced at least one definitely related AE, and the five definitely-related reported AEs (0.4% of the total number of reported AEs) belonged to the General disorders and administration site conditions and Skin and subcutaneous tissue disorders System Organ Classes (SOCs). Two participants who received Menomune vaccine (0.1%) experienced at least one definitely related AE, and the two definitely-related reported AEs (0.3% of the total number of reported AEs) belonged to the general disorders and administration site conditions SOC.

The nature, treatment relatedness and severity of the AEs were not different between the Menactra vaccine and the Menomune vaccine in adults. Out of 3204 adolescent participants who received Menactra vaccine, 926 (28.9%) presented 1327 unsolicited AEs during Day 0 to Day 28 after vaccination, while 397 participants out of 1411 who received Menomune vaccine (28.1%) presented 570 unsolicited AEs during Day 0 to Day 28 after vaccination. These events belonged to all SOCs, but Respiratory, thoracic and Mediastinal disorders, Infections and infestations, Musculoskeletal and connective tissue disorders, Gastrointestinal disorders, and Injury, poisoning and procedural complications accounted for the majority of events reported. Only 0.7% of Menactra vaccine and Menomune vaccine recipients reported at least one severe unsolicited AE between Days 0 and Day 28 following vaccination. There were 28 severe unsolicited AEs during Day 0 to Day 28 in Menactra vaccine recipients (2.1% of the total number of reported AEs) which can be compared to 13 severe unsolicited AEs during Day 0 to Day 28 reported in Menomune vaccine recipients (2.3% of the total number of reported AEs). The most frequent severe unsolicited AEs during Day 0 to Day 28 could not be assigned to one specific SOC but belonged to several different SOCs. Seven participants reported Musculoskeletal and connective tissue disorders, Nervous system disorders, General disorders and administration site conditions, Skin and subcutaneous tissue disorders and Psychiatric disorders SOCs. None of the Menomune vaccine recipients experienced at least one definitely related AE.

The nature, treatment relatedness and severity of the AEs were not different between adolescent recipients of the Menactra vaccine and the Menomune vaccine in. Out of 1848 children who received the Menactra vaccine, 657 (35.6%) presented 1109 unsolicited AEs during Days 0 to 28 after vaccination. A similar number, 611 participants out of 1718 who received the Menomune vaccine (35.6%) presented 1044 unsolicited AEs during Day 0 to Day 28 after vaccination. As expected in subjects belonging to this age group, Infections and infestations, Respiratory, thoracic and mediastinal disorders and Gastrointestinal disorders accounted for the majority of events reported. Only 0.9% and 0.5% of Menactra vaccine and Menomune vaccine recipients, respectively, reported at least one severe unsolicited AE during Day 0 to Day 28 after vaccination. There were 21 severe unsolicited AEs during Day 0 to Day 28 in Menactra vaccine recipients (1.9% of the total number of reported AEs). This can be compared to 10 unsolicited AEs during Day 0 to Day 28 which were considered severe in Menomune vaccine recipients (1.0% of the total number of reported AEs). The infections and infestations SOC accounted for the most frequent and severe unsolicited AEs during Day 0 to Day 28. Thirteen participants who received

Menactra vaccine (0.7%) experienced at least one definitely related AE, and the thirteen definitely-related reported AEs (1.2% of the total number of reported AEs) belonged to the General disorders and administration site conditions. (n=8), Infections and infestations (n=2), Musculoskeletal and connective tissue disorders. (n=1), Nervous system disorders (n=1), and Skin and subcutaneous tissue disorders. (n=1) SOCs. Five participants who received Menomune vaccine (0.3%) experienced at least one definitely related AE (0.5% of the total number of reported AEs) which belonged to the General disorders and administration site conditions. (n=4), and Skin and subcutaneous tissue disorders (n=1) SOCs (Table 39). The nature, relatedness to vaccine, and severity of the AEs in children were not different in the Menactra vaccine and the Menomune vaccine groups.

**Serious Adverse Events and Deaths**

***Menactra Vaccine Used in Meningococcal Vaccine-Naïve Populations***

*Unsolicited Significant Adverse Events Day 29- Month 6 after Vaccination*

Out of 2766 adults participants who received Menactra vaccine, 122 (4.4%) presented 156 unsolicited significant AEs between Day 29 to Month 6 after vaccination, while 79 participants out of 1526 who received Menomune vaccine (5.2%) presented 109 unsolicited significant AEs Day 29 to Month 6 after vaccination. Musculoskeletal and connective tissue disorders, injury, poisoning and procedural complications, pregnancy, puerperium, and perinatal conditions, reproductive system and breast disorders, skin and subcutaneous tissue disorders, and infections and infestations accounted for the majority of events reported. Only 1.0% and 1.3% of Menactra vaccine and Menomune vaccine recipients, respectively, reported at least one severe unsolicited significant AE during Day 29 to Month 6 after vaccination. Of the total unsolicited significant AEs reported among the Menactra vaccine recipients during Day 29 to Month 6, 34 (21.8%) were categorized as severe in intensity. Among Menomune vaccine recipients, 27 (24.8%) of the unsolicited significant AEs reported were categorized as severe in intensity. No particular SOC could be identified as accounting for the most severe unsolicited AEs Day 29 to Month 6. There were no reports of related AEs in either Menactra or Menomune vaccine recipients during this time period. The nature, relatedness to vaccine, and severity of the AEs in adults were not different between the Menactra vaccine and the Menomune vaccine.

Out of 2687 adolescent participants who received the Menactra vaccine, 195 (7.3%) presented 269 unsolicited significant AEs Day 29 to Month 6 after vaccination, while 87 out of 1397 participants who received the Menomune vaccine (6.2%) presented 113 unsolicited significant AEs between Day 29 and Month 6 after vaccination. Infections and infestations, Injury, poisoning and procedural complications, Skin and subcutaneous tissue disorders, and Respiratory, thoracic and mediastinal disorders accounted for the majority of SOC events reported. Only 0.7% and 0.6% of Menactra vaccine and Menomune vaccine recipients, respectively, reported at least one severe unsolicited significant AE during Day 29 to Month 6 after vaccination. There were 22 severe unsolicited significant AEs during Day 29 to Month 6 reported in Menactra vaccine recipients (8.2% of the total number of reported AEs). This can be compared to10 severe unsolicited significant AEs between Day 29 and Month 6 reported in Menomune vaccine recipients (8.8% of the total number of reported AEs). The most frequent severe unsolicited significant AE during Day 29 to

Month 6 could not be assigned to one specific SOC. There were no reports of treatment related AEs in either Menactra or Menomune vaccine recipients during this time period. In adolescents, the nature, relatedness to vaccine, and severity of the AEs were not different in the Menactra vaccine and the Menomune vaccine groups.

Fifty-six out of 1813 children who received the Menactra vaccine (3.1%) presented 65 unsolicited significant AEs between Day 29 and Month 6 after vaccination, while 53 out of 1689 participants who received the Menomune vaccine (3.1%) presented 68 unsolicited significant AEs in the same time period (Table 36). These events were categorized into a range of SOCs but Skin and subcutaneous tissue disorders, and Infections and infestations accounted for the majority of events reported. Only 0.6% and 0.5% of Menactra vaccine and Menomune vaccine recipients, respectively, reported at least one severe unsolicited significant AE between Day 29 and Month 6 after vaccination. There were 13 severe unsolicited significant AEs reported in Menactra vaccine recipients (20.0% of the total number of reported AEs) and 16 severe unsolicited significant AEs in Menomune vaccine recipients (23.5% of the total number of reported AEs) during this time period. Infections and infestations and Respiratory, thoracic and mediastinal disorders SOCs accounted for the most frequent severe unsolicited significant AEs in the period between Day 29 and Month 6. There were no reports of treatment related AEs in either Menactra or Menomune vaccine recipients during this time period. In children, the nature, relatedness to vaccine, and severity of the AEs were not different in the Menactra vaccine and the Menomune vaccine groups.

***Menactra Vaccine Used in Meningococcal Vaccine-Experienced Populations***

Study MTA15, conducted in the UK, compared the safety profile of Menactra vaccine to that of another polysaccharide-protein conjugated vaccine (*Haemophilus influenzae* type b conjugated vaccine, PRP-T, Hiberix®) when used in children already vaccinated with a monovalent C meningococcal protein-conjugated vaccine.

*Unsolicited Immediate Reactions after Vaccination*

No immediate reactions were observed in any subjects who received either Menactra vaccine or Hiberix vaccine in Study MTA15.

*Solicited Local Reactions Day 0 to Day 7 at the Meningococcal Vaccine Injection Site*

Solicited local reactions at the vaccine injection site were reported by 52.9% and 49.0% of participants who received the Menactra vaccine or the Hiberix vaccine, respectively. Redness at the injection site was the most frequently reported reaction. When considering only the severe solicited local reactions, 9.8% of Menactra vaccine participants and 6.1% of Hiberix vaccine participants reported at least one severe solicited local reaction at the vaccine injection site. Redness at the injection site was the most frequently reported severe solicited local reaction (Table 41).

**Table 41: Number and Percentage of Meningococcal Vaccine-Experienced Children Participants Reporting at Least One Solicited Local Reaction and at Least One Severe Solicited Local Reaction during Days 0-7, by Reaction Type (Safety Population)**

| | MTA15 | | | |
|---|---|---|---|---|
| | Menactra Vaccine | | Hiberix Vaccine | |
| | n/N | % | n/N | % |
| ≥ 1 Reaction | 27/51 | 52.9 | 24/49 | 49.0 |
| Severe* | 5/51 | 9.8 | 3/49 | 6.1 |
| Redness | 21/51 | 41.2 | 17/49 | 34.7 |
| Severe* | 5/51 | 9.8 | 3/49 | 6.1 |
| Swelling | 18/51 | 35.3 | 11/49 | 22.4 |
| Severe* | 4/51 | 7.8 | 2/49 | 4.1 |
| Induration | 19/51 | 37.3 | 12/49 | 24.5 |
| Severe* | 3/51 | 5.9 | 2/49 | 4.1 |
| Pain | 18/51 | 35.3 | 17/49 | 34.7 |
| Severe* | 1/51 | 2.0 | 1/49 | 2.0 |

*Solicited Systemic Reactions Day 0 to Day 7 after Vaccination*

The following table (Table 42) presents the numbers of children reporting more than one solicited systemic reaction and more than one severe solicited systemic reaction within 7 days following an injection of Menactra vaccine or the control vaccine (Hiberix vaccine). Solicited systemic reactions after vaccination were reported by 67.3% and 51.0% of participants who received Menactra vaccine or Hiberix vaccine, respectively. For the two vaccines, irritability was the most frequently reported reaction, followed by anorexia, drowsiness, and diarrhoea. When considering only the severe solicited systemic reactions, 13.5% of Menactra vaccine participant, and 12.2% of Hiberix vaccine participants, reported at least one severe solicited systemic reaction after vaccination. Fever (of any severity) was reported in 8.5% of Menactra vaccine recipients and 6.8% of Hiberix vaccine recipients. Severe fever was reported in 2.1% Menactra vaccine recipients but not in any of the Hiberix vaccine recipients. One episode of seizure (febrile convulsions) was reported in one Menactra vaccine recipient.

**Table 42: Number and Percentage of Meningococcal Vaccine-Experienced Children Participants Reporting at Least One Solicited Systemic Reaction and at Least One Severe Solicited Systemic Reaction during Days 0-7, by Reaction Type**

| | MTA15 | | | |
|---|---|---|---|---|
| | Menactra Vaccine | | Hiberix Vaccine | |
| | n/N | % | n/N | % |
| ≥ 1 Reaction | 35/52 | 67.3 | 25/49 | 51.0 |
| Severe* | 7/52 | 13.5 | 6/49 | 12.2 |
| Fever | 4/47 | 8.5 | 3/44 | 6.8 |
| Severe* | 1/47 | 2.1 | 0/44 | 0.0 |
| Irritability | 29/51 | 56.9 | 17/49 | 34.7 |
| Severe* | 2/51 | 3.9 | 1/49 | 2.0 |
| Drowsiness | 18/51 | 35.3 | 10/49 | 20.4 |
| Severe* | 3/51 | 5.9 | 0/49 | 0.0 |
| Anorexia | 19/51 | 37.3 | 10/49 | 20.4 |
| Severe* | 2/51 | 3.9 | 1/49 | 2.0 |
| Vomiting | 4/51 | 7.8 | 2/49 | 4.1 |
| Severe* | 2/51 | 3.9 | 0/49 | 0.0 |
| Diarrhea | 6/51 | 11.8 | 8/49 | 16.3 |
| Severe* | 0/51 | 0.0 | 0/49 | 0.0 |
| Rash | 3/52 | 5.8 | 5/49 | 10.2 |
| Seizures | 1/51 | 2.0 | 0/49 | 0.0 |

*Unsolicited Adverse Events Day 0-Day 28 after Vaccination.*

Of 51 children who received Menactra vaccine, 29 (56.9%) presented 45 unsolicited AEs during Day 0 to Day 28 after vaccination. In comparison, 31 out of 47 (66.0%) Hiberix vaccine recipients presented 51 unsolicited AEs in the same time period. In this age group, infections and infestations accounted for the majority of events reported. During Day 0 to Day 28 after vaccination, 5.9% and 6.4% of Menactra vaccine and Hiberix vaccine recipients, respectively, reported at least one severe unsolicited AE. There were three severe unsolicited AEs during Day 0 to Day 28 in Menactra vaccine recipients (6.7% of the total number of reported AEs) and five unsolicited AEs during Day 0 to Day 28 were severe in Hiberix vaccine recipients (9.8% of the total number of reported AEs). The infections and infestations SOC accounted for the most frequent severe unsolicited AEs during Day 0 to Day 28. One participant vaccinated with Hiberix vaccine (2.1%) experienced at least one definitely related AE (2.0% of the total number of reported AEs) which belonged to the general disorders and administration site conditions SOC. The nature, relatedness to vaccine and severity of the AEs were not different in children given the Menactra vaccine or the Hiberix vaccine.

### *Menactra Vaccine and Menomune Vaccine Comparisons*

Most of the statistical comparisons of the safety profile of Menactra vaccine versus Menomune vaccine were based on the proportion of participants presenting at least one severe solicited systemic reaction during Day 0 to Day 7. Severe solicited reactions were selected because they were considered the most clinically relevant following vaccine

administration. The results of all these statistical comparisons are presented in the following table (Table 43).

**Table 43: Results of Statistical Comparisons of Safety**

| Population | Study | Objective | Endpoint definition and hypothesis tested | Observed delta | Upper Limit of the 95% two-sided CI | Test outcome |
|---|---|---|---|---|---|---|
| Adult | MTA09 | Primary | Upper limit of the two-sided 95% CI* of the ratio of % of participants presenting at least one severe solicited systemic reaction during Days 0-7 (Menactra vaccine divided by Menomune vaccine) is less than 3. | 1.465 | 2.28 | Success |
| | MTA14 | Secondary (third) | Upper limit of the two-sided 95% CI of the difference in % of 26-55-year-old participants presenting at least one severe solicited systemic reaction during Days 0-7 (Menactra vaccine [all consistency lots pooled] minus Menomune vaccine) is less than 10 percentage points. | -3.3 | -1 | Success |
| | | | | | | |
| Adolescent | MTA02 | Secondary | Upper limit of the two-sided 95% CI* of the difference in % of participants presenting at least one severe solicited systemic reaction during Days 0-7 (Menactra vaccine minus Menomune vaccine) is less than 10 percentage points. | -0.21 | 2.37 | Success |
| | MTA04 | Primary | Upper limit of the two-sided 95% CI of the ratio of % of participants presenting at least one severe solicited systemic reaction during Days 0-7 (Menactra vaccine divided by Menomune vaccine) is less than 3. | 1.662 | 2.56 | Success |
| | | | | | | |
| Children | MTA08 | Primary | Upper limit of the two-sided 95% CI of the ratio of % of participants presenting at least one severe solicited systemic reaction during Days 0-7 (Menactra vaccine divided by Menomune vaccine) is less than 3. | 1.017 | 1.37 | Success |
| | 603-02 | Secondary | Upper limit of the two-sided 95% CI of the ratio of % of participants presenting at least one fever episode ≥ 38.0°C (axillary) during Days 0-7 (Menactra vaccine divided by Menomune vaccine) is less than 3. | 0.6886 | 1.22 | Success |

* Two-sided 90% CI (as stated in the protocol) was tested first and two-sided 95% CI (as requested by CBER) was tested second.

In the three populations, all the statistical comparisons testing the non-inferiority of the Menactra vaccine compared to the Menomune vaccine with respect to the occurrence of severe solicited systemic reactions during Day 0 to Day 7 were successfully met.

**Summary of Safety data from Study 603-1 (Safety population)**

Study 603-1 also collected safety data for the different dosages of Menactra. No immediate reactions were reported within the first 30 minutes following administration of the three

dosage formulations. The incidence of solicited local reactions increased significantly with increasing Menactra vaccine doses. In the 1 µg, 4 µg and 10 µg dosage groups, at least one local reaction was reported by 58.6% (17/29), 83.3% (25/30), and 93.3% (28/30) of participants, respectively (p = 0.004, Fisher's exact test; p = 0.001, Cochran-Armitage trend test). The most commonly reported local signs were erythema and swelling/hardness, with the majority of local signs described as ≤ 1 inch in diameter. The most commonly reported local symptoms were tenderness upon touch and pain/soreness, with the majority of local symptoms described as mild. Across all three formulations, most reported local reactions had resolved by Day 3 following vaccine administration. In the 1 µg, 4 µg, and 10 µg dosage groups, at least one solicited systemic reaction was reported by 41.4% (12/29), 50.0% (15/30), and 46.7% (14/30) of participants, respectively; these differences were not statistically significant. The solicited systemic reactions of malaise and headache were reported most commonly. At all dosage levels, the majority of reported solicited systemic reactions were mild and had resolved by Day 3 following vaccine administration. Only one of the 90 adult participants reported severe solicited local and systemic reactions. During the study, there was one report of an unsolicited adverse event (a female participant in the 4 µg group experienced a urinary tract infection thought to be unrelated to treatment). There were no serious adverse events reported during the study. Significant laboratory abnormalities were observed in participants in each of the three dosage groups, but in general, these were present in both the pre- and postvaccination samples. Three participants displayed a similar local and systemic reaction profile involving chills, arthralgia and malaise which had resolved two days after vaccine administration together with local injection site reactions that had resolved by the Day 4 follow-up visit.

**Deaths**

Two deaths occurred during this clinical program, both during Study MTA14. Both events were considered as unrelated to vaccination.

**Other Serious Adverse Events**

The number of participants who presented at least one SAE during study enrollment together with the total number of SAEs reported is presented in Table 44.

**Table 44: Number of Participants with at Least one SAE and Total Number of SAEs Reported in each Population (Safety Populations)**

| Population | Study | Menactra vaccine recipients | | Menomune vaccine recipients | |
|---|---|---|---|---|---|
| | | Number of subjects with at least one SAE n/N (%) | Number of SAEs | Number of subject with at least one SAE n/N (%) | Number of SAEs |
| Adults | MTA09 | 23/1384 (1.7) | 26 | 20/1170 (1.7) | 25 |
| | MTA14 | Lot 1: 12/527 (2.3)<br>Lot 2: 5/528 (0.9)<br>Lot 3: 5/527 (0.9) | 15<br>6<br>5 | 12/458 (2.6) | 19 |
| | MTA11 | 1/469 (0.2) | 1 | NA | NA |
| **Total** | | **46** | **53** | **32** | **44** |
| Adolescents | MTA02 | 5/440 (1.1) | 6 | 1/441 (0.2) | 1 |
| | MTA04 | 22/2270 (1.0) | 22 | 6/972 (0.6) | 6 |
| | MTA12 | 3/1019 (0.3) | 6 | NA | NA |
| **Total** | | **30** | **34** | **7** | **7** |
| Children | 603-02 | 17/696 (2.4) | 28 | 7/702 (1.0) | 15 |
| | MTA08 | 11/1712 (0.6) | 11 | 11/1519 (0.7) | 13 |
| | MTA15 | 1/52 (1.9) | 2 | NA | NA |
| **Total** | | **29** | **41** | **18** | **28** |
| | | | | | |
| **Grand Total** | | **105** | **128** | **57** | **79** |

During the nine clinical studies performed in participants aged 2 to 55 years, 1.8% (105/10100) of participants who received Menactra vaccine and 1.1% (57/5262) of participants who received Menomune vaccine experienced at least one SAE. Two SAEs, that occurred in Menactra vaccine participants (in Studies MTA04 and MTA15) were assessed by the investigators as possibly vaccine related. One was a case of severe distal oesophagitis after a Menactra vaccination. This patient had also self medicated with Tylenol, ibuprofen and naproxen for a back injury just prior. The other subject was a 2-year-old male who experienced a febrile convulsion one day post-vaccination while enrolled in Trial MTA15. The patient also had a respiratory tract infection at the time of vaccination and past history included three previous febrile convulsions. The subject recovered without sequelae from this event and continued in the trial.

### Overdose

By accident, four subjects in Studies MTA11and MTA12 received two consecutive injections of Menactra vaccine one month apart. In all four subjects, the safety profile (immediate reactions, solicited local and systemic reactions, unsolicited AEs during Day 0 to Day 28) observed after the second Menactra vaccine injection was similar to that observed after a single dose of vaccine.

### Safety in Special Populations

#### *Use in Pregnancy and Lactation*

The use of Menactra vaccine has not been studied in pregnant females, but during this clinical program several adults and one adolescent became pregnant during their

participation in the study. Data collected did not identify an elevated risk of pregnancy complications in these women.

The use of Menactra vaccine has not been studied in breastfeeding women.

**Immunological Events**

None specifically identified.

**Safety Related to Drug-Drug Interactions and Other Interactions**

The safety profile of Menactra vaccine when co-administered with other drugs has not been studied in the development program. The safety profile of Menactra vaccine when co-administered simultaneously (or administered with a one-month delay) with other vaccines has been investigated in two studies:

• In Study MTA11 with the Typhim Vi vaccine in adults. The frequency of solicited local reactions at the Menactra vaccine injection site was similar in participants who received Menactra vaccine alone one month after Typhim Vi vaccine (47.2%) and in participants who received Menactra vaccine concomitantly with Typhim Vi vaccine (51.3%). The frequency of solicited systemic reactions was higher in participants who received Menactra vaccine concomitantly with Typhim Vi vaccine (60.5%) than in participants who received Menactra vaccine alone one month after Typhim Vi vaccine (48.1%).

• In Study MTA12 with the Td vaccine in adolescents. The frequency of solicited local reactions at the Menactra vaccine injection site was similar in participants who received Menactra vaccine alone one month after Td vaccine (57.0%) and in participants who received Menactra vaccine concomitantly with Td vaccine (58.0%). Solicited local reactions were more common at the Typhim Vi vaccine injection site than at the Menactra vaccine site. The most common reaction reported was pain and it was mostly mild in severity and had resolved within 2 days. The frequency of solicited systemic reactions was higher in participants who received Menactra vaccine concomitantly with Td vaccine (58.6%) than in participants who received Menactra vaccine alone one month after Td vaccine (35.8%). Subjects who received Td vaccine alone showed similar rates of solicited systemic reactions to subjects who received Menactra vaccine concomitantly with Td vaccine.

**Discontinuation Due to Adverse Events**

Among all participants enrolled and who were considered in the safety populations, the study completion rates for Menactra vaccine recipients ranged from 90.9% to 94.0% for adults, from 96.6% to 99.1% for adolescents, and from 95.4% to 100% for children.

Similarly, the study completion rates for Menomune vaccine recipients ranged from 92.8% to 93.9% for adults, from 98.6% to 98.9% for adolescents, and from 95.4% to 100% for children. The main reason for study withdrawals was 'lost to follow-up' rather than an adverse reaction. Most of the participants who were lost to follow-up failed to provide safety data at the 6-month safety contact. Only one Menactra vaccine participant (Caucasian female in Study MTA14 who died due to a motor vehicle accident) and one Menomune vaccine participant (Caucasian male in Study MTA14 who died due to a drug overdose) did not complete the study due to an AE. Both events were considered unrelated to the study vaccine.

**Post Marketing Experience**

Menactra vaccine was licensed in January 2005 in the United States (US) and in May 2006 in Canada. In both countries it is currently indicated for active immunization of individuals 2 through 55 years of age for the prevention of invasive meningococcal disease caused by *Neisseria meningitidis* serogroup A, C, Y and W-135. In the US, the age indication for use of Menactra was expanded to include children 2 through 10 years on age in October 2007. Since Menactra vaccine was first licensed, a total of 22.74 million doses had been distributed through the end of December 2008: 22,529,306 doses (99%) in the US; 194,019 doses in Canada; 19,000 doses in Saudi Arabia and 51 doses in France. Assuming that patients received one dose, the doses distributed were administered to about 22.74 million patients. An estimate of the profile (age and gender) of the population receiving Menactra vaccine in the US is provided from the insurance claims data based on the private sector reimbursement/claims received from Surveillance Data, Inc; (SDI), and from the US based post-licensure safety surveillance study of routine use of Menactra vaccine in recipients 11 to 55 years of age (MTA30), as shown in Table 45. The majority (95%) of doses were administered to adolescents 11 through 18 years of age in accordance with the Center for Disease Control's (CDC) Advisory Committee on Immunization Practices (ACIP) recommendations in the US.

**Table 45: Post-Marketing Exposure by Age and Gender - Data from MTA30**

| Age Groups (Years) | Female | Male | Total |
|---|---|---|---|
| < 11 | 72 | 77 | 149 |
| 11-16 | 10,311 | 11,367 | 21,678 |
| 17-18 | 4,580 | 3,801 | 8,381 |
| 19-29 | 457 | 370 | 827 |
| 30-55 | 431 | 376 | 807 |
| >55 | 45 | 35 | 80 |
| Total | 15,896 | 16,026 | 31,922 |

**Post-Marketing Safety Profile**

Over the period available for review, 582 medically-confirmed case reports following Menactra vaccine administration and meeting the International Conference on Harmonization (ICH) criteria to be included in Periodic Safety Update Reports (PSURs) were received by the sponsor's Global Pharmacovigilance Department (GPVD): 562 from health care professionals and health authorities, and 20 from clinical trials. These cases involved 1,526 AEs, among them 511 (33.5%) were SAEs. Out of the 582 cases, 268 (46%) were serious. In addition to the medically-confirmed reports, there were 21 consumer reports.

The general safety profile of Menactra vaccine during this period of time shows that a predominance of the AEs (>10%), regardless of the seriousness, fall under the MedDRA SOCs 'Nervous System Disorders', 'General Disorders and Administration Site Conditions' and 'Musculoskeletal and Connective Tissue Disorders'. The SOCs listed below are those encompassing at least 5% of the AEs reported:

- Nervous System Disorders: 394 (25.8%) AEs

- General Disorders and Administration Site Conditions: 379 (24.8%) AEs

- Musculoskeletal and Connective Tissue Disorders: 186 (12.2%) AEs

- Gastrointestinal Disorders: 107 (7%) AEs

- Infections and Infestations: 94 (6.1%) AEs

- Skin and Subcutaneous Tissue Disorders: 82 (5.4%) AEs

The distribution of the serious AEs by SOC also indicates that the SOC 'Nervous system disorders' had the highest number of SAEs reported. The SOCs listed below are those encompassing at least 5% of the SAEs reported:

- Nervous System Disorders: 207 (40.5%) AEs

- Infections and Infestations: 53 (10.4%) AEs

- Musculoskeletal and Connective Tissue Disorders: 51 (10%) AEs

- General Disorders and Administration Site Conditions: 36 (7%) AEs

There were safety communication alerts made by the FDA and CDC (30 September 2005 and 20 October 2006) and the three Morbidity and Mortality Weekly Report (MMWR) communications (October 2005, April 2006 and October 2006 respectively[24,25]), regarding the possible association of GBS with Menactra vaccine administration. Table 46 displays the most frequently reported AEs, received from all sources since licensure through 13 January 2009.

Overall, the majority of the most frequently reported AEs following administration of Menactra vaccine are listed in the Company Core Safety Information (CCSI) or they correspond to potential signs and symptoms of more serious conditions already included in the CCSI. 'Convulsion' is not listed in the current approved CCSI. It remains closely monitored by the sponsor. Below are the labeling changes that were made to the CCSI during the period under review from information gathered from post-marketing surveillance. The following AEs have been added to the section 'Data from Post-marketing Surveillance:

- Immune System disorders

  Hypersensitivity reactions such as anaphylactic/anaphylactoid reaction, wheezing, difficulty breathing, upper airway swelling, urticaria, erythema, pruritus, hypotension

- Nervous system disorders

  Guillain-Barré syndrome, vasovagal syncope, facial palsy, transverse myelitis, acute disseminated encephalomyelitis.

[24]CDC. Guillain-Barré syndrome among recipients of Menactra® meningococcal conjugate vaccine---United States, June--July 2005. MMWR 2005;54:1023--5. Accessed at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5440a6.htm

[25]CDC.Update: Guillain-Barré Syndrome Among Recipients of Menactra® Meningococcal Conjugate Vaccine-United States, June 2005-September 2006. October 20, 2006 / 55(41);1120-1124, accessed at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5541a2.htm

- Musculoskeletal and connective tissue disorders

Myalgia.

The following changes (addition) were also made to the 'Contraindications' and 'Warnings' sections in response to reports of GBS, including two cases with a personal or family (mother) history of GBS:

Known history of GBS is a contraindication to vaccine administration.

GBS has been reported in temporal relationship following administration of Menactra. Based on an evaluation of post-marketing adverse events, a slight increase in the number of GBS reports was observed following administration of Menactra. However, because of the inherent limitations of spontaneous safety reporting, this is not confirmatory of an increased risk and these findings should be viewed with caution. Persons previously diagnosed with GBS should not receive Menactra.

**Table 46: Summary Table of the Most Frequently Reported AEs Following Menactra Vaccine Administration, 14 January 2005 to 13 January 2009**

| Rank[1] | AE MedDRA Preferred Term, regardless of seriousness | n [2] | Rank | AE MedDRA Preferred Term, SAEs only | n [2] |
|---|---|---|---|---|---|
| 1 | Pyrexia | 120 | 1 | Guillain-Barré syndrome | 53 |
| 2 | Headache | 104 | 2 | Syncope / Syncope vasovagal / Loss of consciousness | 35 |
| 3 | Injection site reaction (all forms) [3] | 103 | 3 | Convulsion [6] | 20 |
| 4 | Vomiting / Nausea | 58 | 4 | Meningitis meningococcal / Meningococcal bacteraemia / Meningococcal infection / Meningococcal sepsis [7] | 15 |
| 5 | Guillain-Barré syndrome | 53 | 5 | Facial Palsy | 14 |
| 6 | Fatigue / Asthenia | 48 | | | |
| 6 | Paraesthesia [4] / Hypoaesthesia [5] | 48 | | | |
| 7 | Syncope / Syncope vasovagal / Loss of consciousness | 39 | | | |
| 8 | Myalgia | 36 | | | |
| 9 | Dizziness / Vertigo | 34 | | | |

1 This table does not consider the new important information received between the date of this report (that is, of the most recent PSUR prepared) and the date of finalisation of the Common Technical Document (CTD) report.

2 Includes diagnosis and events, but excludes symptoms.

3 Injection site reaction includes the following MedDRA[26] preferred terms (PTs): Injection site inflammation (n=36), Injection site reaction (n=20), Injection site pain (n=16), Injection site erythema (n=10), Injection site swelling (n=4), Injection site rash (n=3), Injection site cellulitis (n=2), Injection site induration (n=2), Injection site pruritus (n=2), Injection site urticaria (n=2), Injection site warmth (n=2), Injection site atrophy (n=1), Injection site haematoma (n=1), Injection site mass (n=1), Injection site movement impairment (n=1).

4 Paraesthesia includes the MedDRA PTs Paraesthesia (n=28) and Paraesthesia oral (n=2)

5 hypoaesthesia includes the MedDRA PTs Hypoaesthesia (n=16) and Hypoaesthesia facial (n=2)

6 Convulsion includes the following MedDRA PTs: Convulsion (n=14), Grand mal convulsion (n=5), Epilepsy (n=1)

7 Most cases corresponded to vaccine failure

### Important recent post-marketing data

New important information was received between the date of this submission (and that of the most recent PSUR prepared) and the date of finalization of the CTD report regarding the following AEs of special interest:

- GBS: Information provided from the CDC in March 2009 concerned two new reports of confirmed GBS within 6 weeks of vaccination and one report originally confirmed by CISA (Clinical Immunization Safety Assessment network) as GBS but subsequently determined to not meet the criteria for GBS. This information was considered in the analysis of the

[26] MedDRA is the acronym for Medical Dictionary for Regulatory Activities. It is an international terminology employed by the pharmaceutical industry, medical product industry and regulatory agencies throughout the entire drug development process and product postmarketing activities.

reports of GBS following the Acute Disseminated Encephalomyelitis (ADEM): Information from the FDA in April 2009 concerned a total of 14 cases of probable or confirmed ADEM following Menactra vaccine administration from the date of licensure to 31 January 2009. Five out of these fourteen cases had previously been entered in the sponsor's pharmacovigilance database and included in PSURs; four of them reported as ADEM and one as meningoencephalitis. In response to six reports of GBS during the first months of Menactra vaccine distribution, the CCDS was amended in December 2005 to add the event of GBS to the subsection 'Data from Post-marketing surveillance'. The period from vaccination to symptom onset was less than six weeks in these reports. Cumulative data from post-marketing surveillance indicates 62 reports which at one time were coded as GBS (n=60) or MFS (n=2). All but two of these cases occurred in the US and most of them were received through the CDC. For the reports received from the CDC, extensive information was not available to SP. Additionally, any potential report of GBS in the US in Menactra vaccine recipients is referred to the Clinical Immunization Safety Assessment (CISA) network for standardized clinical evaluation of affected patients. These reports are reviewed by CISA using the GBS case definition that is currently under development by The Brighton Collaboration[27]. The outcome of the review by CISA was available for the cases which occurred within 6 weeks of vaccination.

- Of these 62 reports, 37 were confirmed by CISA to be GBS and occurred within 6 weeks of vaccination. Some 33 were among adolescents 11 to 19 years of age. In the four other cases, patients were 20 to 43 years of age. Three of these four cases were confounded by the co-administration of at least one other vaccine. Two patients had a recent history of upper respiratory infection (URI) and concomitant pneumonia or a recent travel to Asia with diarrheal illness prior to the symptom onset.
- Some 12 reports which occurred within 6 weeks of vaccination were reviewed by CISA and determined to not be GBS. Patients were 12 to 17 years of age. Seven cases were confounded by the co-administration of another vaccine.
- Eight reports occurred more than 6 weeks after vaccination. Patients were 12 to 18 years of age. Five cases were confounded by the co-administration of at least one other vaccine. In four cases, patients had a preceding respiratory illness (n=1), URI symptoms (n=1), urinary tract infection, sinus infection and otitis media (n=1) or viral syndrome (n=1). One patient had Lyme disease and in another case GBS was determined to be probably due to Epstein-Barr virus infection. One patient had history of Bell's palsy.
- Two were reports of MFS which occurred more than 6 weeks after vaccination. Patients were 16 and 18 years of age. The time to onset ranged from 3 months to more than 4 months after vaccination. One patient had also received Human papillomavirus vaccine (HPV) and had a history of Bell's palsy.
- Two reports were from Canada and were not reviewed by CISA. Patients were 9 and 46 years of age. Both cases were confounded by the administration of an

[27] The Brighton Collaboration is an international voluntary collaboration that aims to facilitate the development, evaluation, and dissemination of high-quality information about the safety of human vaccines.

influenza virus vaccine. The time to onset was of 4 and 18 days after vaccination, respectively.

- One was a report with symptom onset prior to vaccination.

The key characteristics of the 33 reports of confirmed GBS in patients 11 to 19 years of age within 6 weeks following the administration of Menactra vaccine are as follows:

Twenty-six patients were 15 to 19 years of age and seven were 11 to 14 years of age, with a gender distribution of 20 males and 13 females. The last confirmed case (reported through the VAERS[28]) received Menactra vaccine in August 2008. At this time, of the approximately 19.17 million doses which have been distributed (through the end of July 2008), about 95% of these doses have been administered to patients 11-19 years of age.

The following updated analysis was done similar to the analysis presented by CDC in the MMWR dated 20 October 2006. VAERS reporting rate for confirmed GBS following Menactra vaccine administration was calculated by dividing the 33 confirmed GBS cases in persons aged 11 to 19 years with onset within 6 weeks of vaccination by 25.21 million person-months (that is, 18.21 million doses distributed to persons aged 11 to 19 years multiplied by 6 weeks follow-up per dose). The resulting reporting rate is 0.13 per 100,000 person-months. The reporting rate in the MMWR dated 20 October 2006 was 0.20 per 100,000 person-months.

There has been a significant increase in the number of doses distributed over time, from 3 million doses a year in 2005 to more than 7 million doses a year in 2007 and 2008. This increase in the number of doses distributed was not associated with an increase in the number of reports of GBS. Rather the number of confirmed GBS cases by year remained stable, with 8 cases in 2005, 10 cases in 2006, 8 cases in 2007 and 7 in 2008. This resulted in a marked decrease in the reporting rate over time. The annual reporting rate in 2007 and 2008 was below the estimated background incidence rate of 0.11 per 100,000 person-months used by the CDC for the age group 11 to 19 years of age. More than half of the cases (n=18) were confounded by the co-administration of at least one other vaccine; mainly Tdap[29] (n=10) and Hepatitis A and/or B vaccines (n=9). Twelve cases, however, were preceded by a potential respiratory or gastrointestinal infection. Patients were reported to have a recent history of sore throat (n=1), gastrointestinal signs and symptoms (n=1), viral syndrome/symptoms (n=2), URI (n=5), UR tract symptoms (n=1), cold symptoms/diarrhea (n=1) or had concomitant pneumonia (n=1). Nine cases, among the three with a preceding illness of potential infection, included other potential risk factors, medical history or underlying medical conditions of interest: travel abroad (n=3), potential trauma (n=2), ulcerative colitis (n=1), personal (n=1) or family (n=1) history of GBS, or positive antinuclear antibodies (n=1) 3 months prior to the symptom onset which could indicate various preexisting autoimmune diseases.

[28] Vaccine Adverse Event Reporting System (VAERS) is a passive reporting system, meaning that reports about adverse events are not automatically collected but require a report to be filed to VAERS. VAERS reports can be submitted voluntarily by anyone, including healthcare providers, patients, or family members.

[29] Tdap, sometimes known as dTap, is the acronym for the collective vaccines preventing tetanus, diphtheria, and pertussis (whooping cough).

**Other Demyelinating Neurological Conditions**

Demyelinating neurological conditions other than GBS, including ADEM, transverse myelitis (TM), optic neuritis, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and multiple sclerosis have been reported in Menactra vaccine recipients and continuously closely monitored by the sponsor. The information available was recorded in the sponsor's pharmacovigilance database from 14 January 2005 to 13 January 2009.

Cumulative data from post-marketing surveillance from 14 January 2005 to 13 January 2009 indicates four cases with a mention of ADEM and one case of acute haemorrhagic leukoencephalitis (AHL), which is a very rare and fulminant form of ADEM. Patients were three males and two females, 11 to 19 years of age, and the time to onset ranged from 9 days to 24 days after vaccination. One case involved the co-administration of influenza vaccine. In one case, the diagnosis of ADEM was unlikely and the patient recovered after 36 hours. In the three other cases, the outcome information was either unknown or the patients had not recovered 8 days to 2 months after symptom onset.

In the report of AHL, the patient had a preceding viral gastroenteritis. New important information was received between the DLP of this report and the date of finalization of the CTD report. Information was provided by the FDA which concerned a total of 14 cases of probable or confirmed ADEM that met Level 1 or 2 of diagnostic certainty of the case definition developed by The Brighton Collaboration after Menactra vaccine administration from licensure through 31 January 2009. Four out of the five cases that were already known to the sponsor were among these fourteen cases; the report with a recovery of 36 hours was not included in these fourteen cases. In addition, one case that was previously entered in the sponsor's pharmacovigilance database as meningoencephalitis was among the 14 cases. The key characteristics of these 14 cases are summarised below:

- Patients were 11 to 19 years of age; 10 were males.
- For 11 cases, the time to onset ranged from 7 to 24 days after vaccination (within 2 to 4 weeks); one case occurred 34 days after vaccination; the remaining two cases occurred more than 6 weeks after vaccination (50 days and 70 days, respectively).
- Nine cases were confounded by the co-administration of at least one other vaccine.
- One case had a fatal outcome, which is the report of AHL.

No additional data on these cases were provided. Additional information from an extraction of the VAERS database for the nine cases that were not previously entered in the sponsor's pharmacovigilance database indicated that five of them had a preceding URI (n=2), sick contact with URI (n=1), flu-like symptoms (n=1) or a sore throat (n=1) prior to the symptom onset. For one of these five patients the coding in the VAERS database also indicated that the patient tested positive for Epstein-Barr virus. Comparing to the background rate of 0.4 per 100,000 persons per year (6) the relative reporting rate for ADEM following Menactra vaccination was determined by FDA to be 1.56 (95% CI 0.64 – 2.49) and 1.14 (95% CI 0.49 – 1.78) using a 4 and 6 week risk window respectively for vaccination to onset interval.

***Transverse Myelitis***

Transverse Myelitis (TM) may be a variant of ADEM and typically occurs in patients following viral or bacterial infections. Cumulative data from post-marketing surveillance

from 14 January 2005 to 13 January 2009 indicates 5 reports of TM in Menactra vaccine recipients. Two cases were confounded by the co-administration of at least one other vaccine. In addition to these 5 reports, there was one case reported to have clinical, radiologic (attenuation at T2-T3 level) and cerebrospinal fluid findings consistent with a demyelinating or infectious process of the spinal cord. The patient was 20 years of age and the time to onset was 11 days after a concomitant administration of Menactra vaccine and Tdap. No definite diagnosis, however, was available.

### *Optic Neuritis*

Cumulative data from post-marketing surveillance from 14 January 2005 to 13 January 2009 indicates four reports of optic neuritis in Menactra vaccine recipients. The time to onset ranged from 7 to 26 days after vaccination. Two cases were confounded by the co-administration of at least one other vaccine. Two cases, including one reported as a possible mild retrobulbar optic neuritis, were poorly documented.

### *Chronic Inflammatory Demyelinating Polyneuropathy*

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a chronic relapsing demyelinating polyneuropathy or an autoimmune neurological disease that shares clinical features of GBS, but is thought to be a distinct entity from GBS. Cumulative data from post-marketing surveillance from 14 January 2005 to 13 January 2009 indicates three reports of CIDP in Menactra vaccine recipients.

### *Multiple Sclerosis*

Cumulative data from post-marketing surveillance from 14 January 2005 to 13 January 2009 indicates a single report of multiple sclerosis (MS) in a Menactra vaccine recipient. This case was an 18-year-old female patient and occurred, 167 days after she had received Menactra vaccine and Hepatitis A vaccine 2 days apart. The patient had no reported medical history. MRI of the brain showed multiple white matter lesions in a pattern highly suggestive of MS. The MS panel[30] was positive for cerebrospinal fluid (CSF) oligoclonal bands. Approximately 3.5 months after the symptom onset, the patient was in remission.

### Other Neurological Conditions (Non-demyelinating)

Neurological conditions other than GBS and other demyelinating conditions have been reported in Menactra vaccine recipients. The information presented in this section pertains to the serious neurological AEs that led to labeling changes to the CCDS of Menactra vaccine (facial palsy and vasovagal syncope) as well as the event of convulsion which is still closely monitored by the company. An updated analysis of these AEs following the administration of Menactra vaccine is provided for the time period between 14 January 2005 and 13 January 2009.

### *Facial Paralysis / Bell's Palsy*

The incidence of Bell's palsy in the US is estimated to be 13 to 42.8 cases per 100,000 person-years. In response to reports of Bell's palsy or facial paralysis, the CCDS of Menactra vaccine was amended on 14 December 2006 to add the event of facial palsy to the subsection 'Data from Postmarketing surveillance'. Cumulative data from post-marketing surveillance from 14 January 2005 to 13 January 2009 indicates 28 reports with a mention of Bell's palsy or facial paralysis. Out of these reports:

[30] An MS panel is a set of tests that simultaneously measure and compare the cerebrospinal fluid (CSF) and serum protein levels and immune system activity.

- Eight occurred in the context of confirmed GBS (n=6) or other peripheral neuropathies (n=2).
- Patients were 12 to 19 years of age.
- Seven cases occurred within 6 weeks of vaccination; in the remaining case the time to onset of 7.5 months after vaccination makes the potential association between the reported events and the vaccine highly unlikely.
- All but one of the cases were confounded by the co-administration of at least one other vaccine or Tuberculin PPD[31] administration prior to the symptom onset. One female who was a study participant in a HPV study, developed Bell's palsy five months after the third dose of the investigational HPV type 16 and 18 vaccine, nine months after Menactra vaccine, and 10 months after Tdap. Limited information was available but there was little possibility that the reported event was caused by Menactra vaccine.

The key characteristics of the 19 other cases are summarised below:

- All of these cases occurred in patients 11 to 19 years of age and most of them (n=11) were confounded by the co-administration of at least one other vaccine, mainly Tdap (n=7).
- For 12 cases, the time to onset ranged from the day of vaccination to 8 days after vaccination. In 6 cases the time to onset ranged from 11 to 31 days whereas in the remaining case it occurred more than 6 weeks after vaccination.
- Four cases were determined to have occurred in the context of Lyme meningitis, aseptic meningitis, and encephalitis with positive titres for Mycoplasma or Ramsey-Hunt syndrome (diagnosis upon admission). Two cases had either a preceding ear infection or concomitant acute otitis media. Three patients had a history of cold sores, shingles or Herpes simplex virus infection as well as a personal (n=1) or family (n=1) history of Bell's palsy.

***Vasovagal Syncope***

In response to reports of syncope shortly after vaccination the CCDS of Menactra vaccine was amended on 14 December 2006 to add the event of vasovagal syncope to the subsection 'Data from Post-marketing surveillance'. Cumulative data from post-marketing surveillance from 14 January 2005 to 13 January 2009 indicates 39 reports consistent with the hypothesis of vasovagal syncope or vasovagal response.

The key characteristics of these cases are summarised below:

- All but one of these cases (where the age was not reported) occurred in patients 11 to 19 years of age. Mainly females (n=28) were involved.
- Most of them (n=25) were confounded by the co-administration of at least one other vaccine, mainly HPV (n=12) and Tdap (n=11), or Tuberculin PPD (n=3).
- For 37 cases, the time to onset ranged from immediately to 40 minutes after vaccination; the two remaining cases occurred the day of vaccination and no precise time to onset was specified.
- In six cases, the patients were admitted to the hospital.

[31] PPD-Protein purified derivative (tuberculosis skin test)

- Four patients had a previous history of fainting either after prior vaccinations (n=2), while giving blood (n=1), or had experienced a prior syncopal episode unrelated to any injection or vaccination (n=1).
- Eight cases involved a fall at times associated with subsequent injuries.
- Eight patients developed seizure-like activity in the context of the vasovagal response

### *Convulsion*

Post-marketing surveillance between 14 January 2005 and 31 January 2008 indicated a total of 19 reports with a mention of convulsion or seizure. All 19 cases occurred in patients 11 to 18 years of age and most of them (n=12) were confounded by the co-administration of at least one another vaccine, most often HPV (n=7), Tdap (n=6) or Hepatitis A vaccine (n=5). In eleven of the cases, the event occurred within 24 hours following vaccination. Of these, seven occurred within few minutes or "shortly" after vaccination. In five cases the time to onset ranged from 1 to 3 days. In the three remaining cases, it occurred more than 3 days or up to 10 days after vaccination. The presence of fever was reported in only two of these cases. All 19 cases were classified according to the case definition of generalized convulsive seizures recommended by the Seizure Working Group within The Brighton Collaboration. Thirteen out of these 19 cases were determined to meet one of the three levels of diagnostic certainty of this case definition. In fifteen reports an alternative etiology and/or risk factor was identified:

## Other Events of Interest

### *Allergic Events*

In response to reports of urticaria, the CCDS was updated on 20 December 2005 to include this event in the 'Post-marketing reports' section. The CCDS was later updated on 3 January 2008 to include additional allergic manifestations such as anaphylactic/anaphylactoid reaction, wheezing, difficulty breathing, upper airway swelling, erythema, pruritus, and hypotension. An assessment was made of the reports of possible anaphylaxis following the administration of Menactra vaccine that were recorded in the sponsor's pharmacovigilance database from 14 January 2005 to 13 January 2009. This review indicates 14 reports of possible anaphylaxis that met the level 1 to 3 of diagnostic of certainty of anaphylaxis proposed by The Brighton collaboration. In one case the patient had a pre-existing latex allergy which is a contraindication to Menactra vaccine administration. In another case the event was thought to be related to allergy to kiwi since percutaneous skin testing revealed positive reaction to kiwi and the patient had eaten a kiwi shortly prior to the symptom onset.

### *Pregnancy*

From 14 January 2005 through to 13 January 2009, the sponsor received 112 reports of inadvertent exposure to Menactra vaccine occurring 30 days before or at any time during pregnancy. Of these reports, 67 (60%) women had received at least one other vaccine or Tuberculin PPD in addition to Menactra vaccine. The exposure to Menactra vaccine mostly occurred during the first trimester of pregnancy. A total of 100 (89.3%) reports were received after vaccination but before the outcome of the pregnancy was known and were classified as prospective reports. Twelve (10.7%) reports were received after the outcome of the pregnancy was known and classified as retrospective reports.

Of the 12 retrospective reports:

- Five of the pregnancies resulted in the birth of five live born infants. No congenital anomalies were reported.
- Two pregnancies were terminated electively. In one report, it was the intent of the subject to terminate the pregnancy but specific information was not available.
- Three reports of spontaneous abortion / miscarriage occurred during the first trimester (0-13 weeks).
- In one case, it is unclear whether the patient actually had a spontaneous abortion at less than 14 weeks of gestation. From follow-up information, assessment reportedly was threatened abortion.
- No fetal deaths occurred.

**Evaluator's Overall Conclusions on Clinical Safety**

From the safety data presented, overall it appears that the Menactra vaccine was well tolerated although local reactions were common. Low level systemic reactions such as headache and fever were also common, especially in children.

- 0.1%, 0.3%, and 0.3% of adult, adolescent, and children, respectively, have presented at least one immediate reaction after vaccination, consisting mostly of injection site reactions and vasovagal events. No anaphylactic reactions were reported.
- 47.2% to 57.6%, 57.0% to 72.4%, and 34.3% to 58.8% of adult, adolescent, and children, respectively, have presented at least one local reaction at the vaccination site.
- 48.1% to 61.9%, 35.8% to 58.6%, and 36.1% to 67.3% of adult, adolescent, and children, respectively, have presented at least one systemic reaction within the 7 days following vaccination.
- 27.9%, 28.9%, and 35.6% of adult, adolescent, and children, respectively, have presented at least one adverse event within the 28 days following vaccination.
- 4.4%, 7.3%, and 3.1% of adult, adolescent, and children, respectively, have presented at least one unsolicited significant adverse event during an additional follow-up period of five months implemented in six of the studies.

Of these, specifically:

- Pain was the most commonly reported solicited local reaction. Severe local reactions of all categories were reported in 1.0 to 2.7%, 1.1% to 2.2%, and 0.4 to 5.1% of adult, adolescent, and children Menactra vaccine recipients, respectively. The median duration of local reactions was approximately 2 days for all participants and the majority of these were reported as mild in severity and as reversible.
- Headache, fatigue, malaise, arthralgia, diarrhea, and anorexia were the most commonly reported solicited systemic reaction(s) in 2.3% to 5.3%, 3.2% to 4.8%, and 4.7% to 13.5% of adults, adolescents, and children. Systemic reactions were more frequent in younger participants. Systemic reactions lasted longer in participants aged 18 to 55 years compared with participants aged 11 to 17 years; the median duration being approximately three days. The majority were reported as mild in severity and as reversible.

- Unsolicited adverse events were for the most part reported as unrelated to treatment and consisted of common medical ailments.
- In addition, when considering the results of the six randomized Menactra vaccine versus Menomune vaccine studies in which a safety comparison was performed, the following conclusions can be drawn:
- Solicited local reactions (and severe solicited local reactions) were more frequently reported in Menactra vaccine recipients than in Menomune vaccine recipients. No effect of age on the incidence of solicited local reactions was observed. Solicited local reactions lasted longer when induced by the Menactra-vaccine than the Menomune vaccine.
- A similar frequency of solicited systemic reactions (and of severe solicited systemic reactions) was noted in Menactra vaccine recipients and Menomune vaccine recipients. Solicited systemic reactions were more frequent in younger Menactra vaccine participants whereas there was no effect of age in Menomune vaccine recipients.
- Unsolicited adverse events were similar in nature and frequency in Menactra vaccine treated recipients compared with Menomune vaccine recipients.
- Solicited local reactions were more frequent in Menactra vaccine recipients compared with Menomune vaccine recipients (increased number of local reactions of slightly longer duration). This may be due to the diphtheria protein.

The systemic safety profiles of Menactra vaccine and Menomune vaccine were similar, and both vaccines were relatively well tolerated. The three randomized, comparative studies with primary safety endpoints demonstrated the non-inferiority of the safety profile of Menactra vaccine to that of Menomune vaccine. The conclusions of the other three randomized comparative studies having secondary safety endpoints were similar.

Overall, rashes tended to be mild, localized maculo-papular reactions and most were at or near the injection site. The remaining rashes occurred in different areas of the body and no clear pattern of rash emerged. Most rashes had resolved within two days after vaccination.

Overall, severe fever after Menactra vaccination was reported in one adult, two adolescents and ten children. During the entire clinical program, only one episode of febrile convulsions was observed in one Menactra-vaccine treated child enrolled in Study MTA15. The frequency of serious adverse events was similar in the two treatment groups. There were no serious adverse events definitely attributable to vaccine administration in any age group.

In the post-marketing data however, a number of other important conditions have emerged which may be related to Menactra vaccination. These occurred with an incidence that would have made them unlikely to be able to detect in the safety studies. Unfortunately the post-marketing reporting is anecdotal, non uniform and contains many confounders such as the administration of other vaccines and intercurrent infections in these patients. For some of these reports, there is minimal clinical information and some fail to fulfill the diagnostic criteria when re-examined. Given this, the relationship is yet to be determined. The most important of these is Guillain-Barre syndrome which has an occurrence post-vaccination that was initially higher than would be epidemiologically

expected[32, 33]. Subsequent data collection over the last three years has shown an incidence close to that background expected incidence. Other demyelinating conditions have also been reported post-Menactra, in particular ADEM, transverse myelitis, optic neuritis and CIDP, as well as Bell's Palsy, convulsion and vasovagal syncope. As mentioned, these reports need further evaluation to assess any relationship to Menactra.

In response to the reports of GBS in Menactra vaccine recipients, the sponsor is supporting an epidemiologic study to further evaluate any potential risk of GBS among vaccinated persons. This study is still under way with data from the second interim study report, dated 5 September 2008 from the Harvard Medical School/Harvard Pilgrim Health Care researchers. A third interim study report dated 11 March 2009 was received. This report included three additional months of data extraction and no confirmed cases of GBS within 42 days following Menactra vaccination were observed.

**List of Questions**

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a "list of questions" to the sponsor is generated.

**Efficacy**

Q: Is there any epidemiological post-marketing data to support the clinical efficacy of Menactra?

**Safety**

Q: Is it possible to have an update on the incidence of neurological events such as Guillain-Barre or other demyelinating conditions, from further collection of data throughout 2009/2010?

Q: Have there been further reports of convulsions in addition to those mentioned in this reports (post-January 2008) following vaccination with Menactra.

The sponsor's responses to these questions are listed under *Sponsors Response* below.

**Clinical Summary and Conclusions**

The data submitted relating to the dose and immunogenicity of Menactra are of good quality and considered adequate. The comparative studies show non-inferiority of Menactra when compared to the Menomune vaccine. The co-administration studies with Td and Typhim Vi show no interference with these vaccines. The safety data also shows a similar safety profile to Menactra with a slightly higher rate of local reactions.

The major clinical issue still to be resolved is the relationship between the neurological events described above and Menactra, in particular with respect to GBS. The case reports

[32]CDC. Guillain-Barré syndrome among recipients of Menactra® meningococcal conjugate vaccine---United States, June--July 2005. MMWR 2005;54:1023--5. Accessed at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5440a6.htm

[33]CDC.Update: Guillain-Barré Syndrome Among Recipients of Menactra® Meningococcal Conjugate Vaccine . United States, June 2005-September 2006. October 20, 2006 / 55(41);1120-1124, accessed at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5541a2.htm

are difficult to assess as the data is non-standardised and sometimes deficient, with many confounders. In a number of cases co-administration of other vaccines had occurred and even the background prevalence has not definitively been determined. Currently the CDC view is that although the incidence of GBS does not appear to be higher in Menactra recipients, the timing of the onset of disease (within 6 weeks) is still of concern.

**Benefit Risk Assessment**

***Benefits***

Menactra appears to be an effective vaccine that is highly immunogenic in adults, adolescents, and children in comparison to Menomune vaccine. In the comparative efficacy studies, all the non-inferiority objectives were met. Its immunogenicity may prove to be better than its existing polysaccharide comparators in clinical practice in that it will be more effective in children and is also likely to be longer lasting. It also appeared from the data to be very effective in priming the immune response. The side effects are typical of vaccines, with the incidence of local and systemic reactions within the first 7 days falling within the expected type and range. Overall Menactra was well tolerated. In relation to safety, all the non-inferiority objectives (the primary or the secondary study objectives) were successfully met. Similar to local reactions, the systemic reactions were well tolerated, generally mild in severity and of a short duration. During the six randomized, comparative studies, unsolicited adverse events that occurred during the first 28 days following a vaccination with Menactra vaccine were of no particular clinical relevance, and the incidence was similar between Menactra vaccine and Menomune vaccine recipients. During the additional 5-month period of clinical follow-up implemented during these randomized, comparative studies, no clinically relevant adverse events occurred.

***Risks***

In each age group, the frequency of solicited local reactions was higher in the Menactra vaccine group than in the meningococcal polysaccharide vaccine group but they were similar to other currently licensed vaccines such as Td and Typhim Vi. The incidence of systemic reactions was similar between the two groups. The use of Menactra vaccine has not been proactively documented in females of childbearing age or in breastfeeding women.

The major risk is that there proves to be a causal relationship between Menactra and GBS or one of the other neurological conditions discussed under *Safety* above. It appears that at this time, no definitive link has been proven and the incidence of GBS is not currently thought to be higher than in the background community, but further data needs to be collected and close monitoring needs to continue.

***Balance***

Overall the post marketing experience with Menactra vaccine over 4 years in the US and Canada, and including more than 22.7 million doses, has confirmed a favorable safety profile although there is a possible relationship to some serious neurological events which needs to be closely monitored.

### *Conclusions*

Overall this vaccine appears from the clinical development program data to be as efficacious and safe as a current comparator, Menomune. Theoretically a conjugate vaccine such as Menactra should have long term advantages over the polysaccharide comparator, Menomune. Menactra does not appear to interfere when co-administered with Td or Typhim V. This should translate into public health benefits from the appropriate use of this vaccine, in 'at risk' groups as discussed above. The current available data does not allow a definitive characterization of the relationship between Menactra vaccine and a number of demyelinating neurological conditions such as GBS. The sponsor is supporting a population-based controlled study to further evaluate any potential risk of GBS among vaccinated persons and this study is currently under way.

**Recommended Conditions for Registration**

Post-marketing data needs to be updated if possible, in relation to the neurological conditions mentioned above.

# V. Pharmacovigilance Findings

## Risk Management Plan (RMP)

A summary of the RMP evaluated by the Office of Product Review (OPR) is presented in Tables 47 and 48 below.

**Table 47: Risk Management Plan Anaphylaxis and Vasovagal Syncope**

| Safety concern | Proposed pharmacovigilance activities (routine and additional) | Proposed risk minimization activities (routine and additional) |
|---|---|---|
| **Important identified risks:**<br>- Vasovagal Syncope<br>- Anaphylaxis | **- Routine Pharmacovigilance activities:**<br>Close monitoring in ongoing trials;<br>Spontaneous reports: enhanced follow-up;<br>Comprehensive evaluation of these events in PSURs;<br>Batch investigation is systematically performed.<br>**- Additional Pharmacovigilance activities:**<br>Post-licensure safety surveillance studies of routine use of Menactra vaccine (MTA30 and MTA38). | - Important identified risks are listed in the Adverse Events section.<br>- For anaphylaxis:<br>Statement in the Contraindications section that a known systemic hypersensitivity reaction to any component of Menactra vaccine or after previous administration of the vaccine or a vaccine containing the same components is a contraindication to vaccine administration.<br>Statement in the Warnings/Precautions section(s) that as vial stoppers contain dry natural rubber latex, caution should be exercised when the vaccine is administered to subjects with known hypersensitivity to latex (vial presentation only).<br>Statement in the Warnings/Precautions section that before the injection, the person responsible for administration must take all precautions known for the prevention of allergic or any other reactions. Appropriate medical treatment and supervision should always be readily available.<br>- Subject's surveillance in a medical care environment for 15 to 30 minutes according to standard and general recommendations on vaccination. |

Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

**Table 48: Risk Management Plan, Guillain-Barre Syndrome, Other demyelinating and non demyelinating neurological conditions, Pregnant or lactating women**

| Safety concern | Proposed pharmacovigilance activities (routine and additional) | Proposed risk minimization activities (routine and additional) |
|---|---|---|
| **Important potential risks:**<br>- Guillain-Barré Syndrome<br>- Other demyelinating neurological conditions including but not limited to Acute Disseminated Encephalomyelitis (ADEM) and Transverse myelitis<br>- Other neurological conditions (non-demyelinating): Facial paralysis, Convulsion | **- Routine Pharmacovigilance activities:**<br>Close monitoring in ongoing trials;<br>Spontaneous reports: enhanced follow-up;<br>Comprehensive evaluation of these events in PSURs;<br>Routine signal detection;<br>Quantitative signal detection using VAERS Database;<br>Specialized AE collection form was designed for GBS.<br>**- Additional Pharmacovigilance activities:**<br>sanofi pasteur is funding a large epidemiological study of risk of GBS after Menactra vaccination based on claims data from several large Managed Care Organizations with a targeted combined membership of over 50 million members. (Harvard Pilgrim Health Care Study);<br>Post-licensure safety surveillance studies of routine use of Menactra vaccine (MTA30 and MTA38) | - Important potential risks are listed in the Adverse Events section.<br>- For Guillain- Barré Syndrome:<br>Statement in the Contraindication section that a known history of GBS is a contraindication to vaccine administration.<br>Statement in the Warnings/Precautions section(s) that persons previously diagnosed with GBS should not receive Menactra vaccine. |
| **Important missing information:**<br>- Pregnant or lactating women<br>- Immunocompromised individuals | - Routine Pharmacovigilance activities for cases reported from special groups<br>- Menactra vaccine Pregnancy Registry | - Statements in the Pregnancy and Lactation sections that Menactra vaccine should be given to a pregnant woman only if clearly needed, and only following an assessment of the risks and benefits.<br>- Statement in the Warnings/Precautions section(s) that no data are available on the use of Menactra vaccine in immunodeficient individuals. If the vaccine is used in persons under immunosuppressive therapy, the expected immune response may not be obtained. In such cases it is recommended to postpone the vaccination until the end of the immunosuppression. |

## Conclusion and Recommendations to the Delegate

This was a well presented RMP with activities to address the important identified and potential safety concerns clearly described. However, issues relating to information on the additional pharmacovigilance (PhV) activities and inclusions in the PI and CMI were noted. Also there was no information on predicted use in Australia.

It was recommended to the Delegate that the sponsor should:

- Provide information on the volume of predicted use in Australia and the basis on which this is derived.
- Provide the final report for Study MTA30 and if not available, specify the date when this will occur;
- Provide the final report for the GBS study and if not available, specify the date when this will occur;
- Specify the criteria for unexpected AEs or a differential pattern of SAEs in Study MTA38 and the types of additional analyses that may be undertaken if these occur;
- Indicate whether Australian women will be included in the pregnancy registry and if not, the reasons for this;
- Indicate how health professionals and consumers are informed of the existence of the pregnancy registry and encouraged to report cases of exposure in pregnancy; and
- Provide information on progression of the OTIS[34] pregnancy project and if this is not occurring, the reason for this.
- Consider reference in the PI to lack of studies in patients with:
  - Renal, hepatic or cardiac impairment.
  - Serious chronic disease.
  - Known HIV positivity or a parent known to be HIV positive.
  - Known hepatitis B or C seropositivity as reported by a parent or legal guardian.
  - Known or suspected impairment of immunologic function.
  - History of cancer or other immunosuppressive disease including known HIV.
- Consider inclusion of use in patients with a bleeding disorder contraindicating IM vaccination in the contraindications.

# VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

### Quality

The administrative, product usage, chemical, pharmaceutical, microbiological and biopharmaceutical data submitted in support of the application have been evaluated. A number of issues were identified during the evaluation of sterility aspects but the evaluation of manufacturing and quality control aspects have now been satisfactorily resolved.

### Nonclinical

Nonclinical data consisted of immunogenicity studies in rodents, a combined acute and repeat dose toxicity study in rats, an antibody transfer study in mice, rats and rabbits and an embryofetal developmental toxicity study in mice. Substantial immunogenicity and bactericidal activity of Men A, C, W-135, Y conjugate vaccine was demonstrated in mice and rats. There are no suitable animal models of N. Meningitidis infection and demonstration of protective efficacy will rely on clinical data. No remarkable systemic or local effects were observed in rats given the clinical IM Menactra dose on two occasions. No remarkable concerns were raised by the embryofetal development study in mice. There are no objections to registration on clinical grounds provided clinical studies support satisfactory efficacy and local effects.

[34] The Organization of Teratology Information Specialists is a non-profit organization made up of individual services (TIS) throughout North America.

## Clinical

The primary clinical data in this submission consist of 11 clinical studies. One Phase I dose escalation study (Study 603-01) was followed by Phase II studies which compared one dose of Men A, C, W-135, Y conjugate vaccine (abbreviated as Menactra) with Men A,C,W-135, Y polysaccharide vaccine/Menomune in adults (Study MTA09), adolescents 11-18 years (Study MTA02) and children 2-10 years (Study 603-02). Other Phase II studies assessed concomitant vaccines in adults and adolescents and Menactra administration in children who had previous MCCV. A Phase III study in adults involved comparison of three lots of Menactra for lot consistency (Study MTA14) and for safety comparison with Menomune. Phase III studies with safety objective were performed in adolescents (Study MTA04) and children 2 to 10 years (Study MTA08).

Serum bactericidal antibody using baby rabbit as source of complement (SBA-BR) was the primary assay used in the development of Menactra. In the development of Men C conjugate vaccines, SBA-BR titres < 1:8 indicated an absence of protection and SBA-BR titres $\geq$ 1: 128 were correlated with SBA-HC deemed to be protective. SBA-BR titres 1:8, 1:16, 1:32 and 1:64 were reassessed with SBA-HC. SBA-BR performed by Sanofi Pasteur was appropriately correlated with WHO ECBS and CDC methods and compared with SBA-HC to further support clinical relevance of SBA-BR results. SBA-BR percentage with $\geq$ 4 fold rise was adequately justified as primary endpoint for comparison of Menactra with Menomune. ELISA IgG and IgM assays were secondary assays.

The clinical development program demonstrated non-inferiority with respect to immunogenicity for Menactra compared to Menomune in adults, adolescents and children, with the primary criteria based on the percentage of subjects with > 4 fold increase in SBA-BR for the four serogroups. Lot consistency in immune response for Menactra was not satisfied for serogroups C and Y but the divergence only occurred at high levels of antibody and is therefore not considered clinically significant. Concomitant administration of Men A, C, Y, W-135 conjugate and Typhim Vi (PS) vaccine and Td vaccine was evaluated with no drug-drug interference seen. Immunogenicity was concluded to be adequate to support registration with potential advantages compared to polysaccharide comparators in children, a likely longer lasting response immune response as well as effectiveness in priming the immune response.

In clinical studies, Menactra was well tolerated but with local and systemic reactions common, especially in children. Solicited local reactions were more frequent in recipients of the Menactra vaccine compared to the Menomune vaccine whereas solicited systemic reactions were similar in Menactra and Menomune recipients. Based on an analysis of severe solicited systemic reactions, Menactra was concluded to be non-inferior to Menomune. The frequency of serious adverse events was similar for Menactra and Menomune, with no serious adverse events definitely attributable to either vaccine in any age group.

In post-marketing data a number of conditions have been reported with an incidence that would have made them unlikely to be detected in clinical studies of safety. The most important of these is considered to be GBS which was initially reported at a higher incidence than epidemiologically expected. There is now experience with 22.7 million doses, predominantly administered to adolescents in USA, and CDC has concluded that the incidence of GBS is not increased in Menactra recipients. The timing of onset within 6 weeks is still a concern in CDC analysis. An epidemiological study (by Harvard Medical School/Harvard Pilgrim Health Care) to further assess the potential risk of GBS is still underway.

The clinical evaluator supported registration with a favourable safety profile although the possible relationship to serious neurological events warrants continuing close monitoring.

## Risk Management Plan

OPR consider that the RMP demonstrates that Sanofi Pasteur is undertaking comprehensive pharmacovigilance and risk management activities. However, as there are ongoing reports of GBS and other neurological disorders associated with the use of the vaccine, a need for continued robust safety monitoring of this risk was highlighted.

OPR made recommendations which need to be fulfilled prior to any registration (see above under *Risk Management Plan*).

## Risk-Benefit Analysis

### *Delegate Considerations*

In Australia, meningococcal diseases is currently caused by serogroups B and C with few cases caused by serogroups A, W-135 and Y. Children under 5 years of age and young adults aged 15 to 24 years are at the highest risk of acquiring meningococcal disease. In Australia, meningococcal C conjugate vaccine (MenCCV) is included in the National Immunisation Program (NIP) as single dose at 12 months of age and a catch up program was conducted in children and adolescents to 19 years of age in 2003. The sponsor's current clinical developmental program has not included any studies comparing Menactra with any MenCCV registered in Australia.

Menactra is proposed for individuals 2 through 55 years of age and is not suitable for current NIP recommendations for prevention of serogroup C disease. Disease surveillance has not to date demonstrated a need for MenCCV booster doses from age 2 years and upwards. If Menactra is registered, a potential population is travellers but only one interaction study with other commonly used travel vaccines has been conducted to date.

The clinical evaluator requested that any epidemiological post-marketing data to support the clinical efficacy of Menactra be submitted and that the sponsor provide an update on neurological events such as GBS from data collected through 2009/2010.

The Delegate concurred with the conclusions of the clinical and RMP evaluators that the immunogenicity data and the favourable safety profile were adequate to support the registration of Menactra for the indications proposed. In view of ongoing reports of GBS and other neurological disorders associated with the use of the vaccine, there is a need for continued robust safety monitoring.

### *Delegate's Proposed Action*

The Delegate proposed to register Menactra indicated for:

*Active immunisation of individuals 2 through 55 years of age for the prevention of invasive meningococcal disease caused by N. meningitidis serogroups A, C, Y and W-135.*

The advice of ACPM was requested.

## Response from Sponsor

Sponsor commented on the following aspects given by the RMP, clinical and non-clinical evaluators and the Delegate.

**Regarding results from the epidemiological study (Harvard Medical School/Harvard Pilgrim Health Care) assessing the potential risk of GBS which is still underway.**

***Sponsor Response:***

Sponsor refers to RMP responses submitted to TGA which includes the final report for the GBS study ("Risk of Guillain-Barré Syndrome Following Meningococcal Conjugate (MCV4) Vaccination").

During post-marketing surveillance since approval of Menactra vaccine, Guillain-Barré Syndrome (GBS) has been reported in some individuals (primarily 11-19 year olds) within 6 weeks of receiving Menactra vaccine. An early evaluation of post-marketing adverse events suggested a potential for an increased risk of GBS following vaccination[35], Nonetheless, after careful deliberation, the US Centers for Disease Control and Prevention (CDC) continued to recommend that all US adolescents and certain individuals with increased meningococcal disease risk be vaccinated with quadrivalent conjugate meningococcal vaccine (MCV4, Menactra vaccine).

Investigators at the Harvard Medical School and Harvard Pilgrim Health Care Institute conducted a multi-site retrospective cohort and nested-case control study ("Risk of Guillain-Barré Syndrome Following Meningococcal Conjugate Vaccination"; NCT00575653) that was based on claims data from multiple Managed Care Organizations in the US. This study, completed in late 2009, involved over 12 million adolescents, of whom 1.4 million received Menactra vaccine, and concluded that there is no evidence of increased risk for GBS associated with the use of Menactra vaccine. In addition, an active sequential safety surveillance (or Rapid Cycle Analysis) conducted by the Vaccine Safety Datalink (VSD) project, a collaborative effort between the CDC and several Managed Care Organizations in the US, reached the same conclusion. These study findings were presented at the CDC's Advisory Committee on Immunization Practices (ACIP) meeting on June 23, 2010. The overall evaluation of post-marketing information did not reveal any new safety concerns.

**Regarding the request to provide the final report for Study MTA30, or if this is not available, provide an interim report and also the protocol including statistical analysis plan for Study MTA38;**

***Sponsor Response:***

The sponsor submitted and interim study report for this study ("Post-Licensure Safety Surveillance Study of Routine Use of Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine (Menactra®)". The protocol for MTA38, "Postlicensure Safety Surveillance Study of Routine Use of Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Vaccine (Menactra®) in Recipients 2 to 10 Years of Age" was provided within the Risk Management Plan (RMP_284, data lock point 13 January 2009, version 1.0,). The sponsor also commented that the Statistical Analysis Plan (SAP) for this study is currently being written. It is anticipated that the SAP will define an unexpected AE as one that appears significantly more often in the investigational than the control group, is plausibly related to vaccination, and is not included in the list of AEs specified in the current approved label. The SAP will likely define "differential pattern of SAEs" similarly. It is anticipated that the SAP will specify that in such case, subgroup analyses will be done to further characterize the AE and regression analyses will be considered to identify predictive factors, if any, for development of the AE.

**Q: Have there been further reports of convulsions in addition to those mentioned in this report (post-January 2008) following vaccination with Menactra®?**

[35] CDC. Update: Guillain-Barré Syndrome Among Recipients of Menactra® Meningococcal Conjugate Vaccine. United States, June 2005-September 2006. MMWR 55(41):1120-1124, 2006.

***Sponsor Response*:**

A comprehensive review of the reports of convulsion in Menactra® recipients was provided in the PSUR17 (submitted to TGA as part of the Response to RMP Evaluation Report dated 20 October 2010) and included cumulative data from post-marketing surveillance from 14 January 2005 through 19 June 2009. In response to this review, the Company Core Data Sheet (CCDS) of Menactra was amended to add the event of convulsion to the section Data from Post-marketing surveillance. The event of convulsion is mentioned in the section 'Adverse Effects - Post-Marketing Reports' of the proposed PI.

To identify further reports of convulsions from the time the cumulative review included in the initial submission was completed (Data through 13 January 2009) until 13 January 2011 (Data Lock Point of the latest PSUR18), the MedDRA Preferred Terms (PTs) belonging to the Standardised MedDRA Query (SMQ) (broad and narrow) for the medical concept of convulsion were queried. MedDRA version 13.1 was the version used for the purpose of this query.

Consistent with the initial submission, the following reports were taken into account: postmarketing spontaneous reports, reports received through health authorities and literature data; fatal serious adverse events (SAEs) and related SAEs that occurred in the context of postlicensure clinical trials conducted in individuals 2 through 55 years of age; and fatal SAEs, related SAEs and unlisted related non-serious AEs that occurred during the US-based post-licensure safety surveillance studies of routine use of Menactra® in recipients 2 through 55 years of age.

Cumulative data over a 2-year additional time period, since 14 January 2009 through 13 January 2011, indicate a total of 12 new reports. During the same time period, approximately 15.3 million doses of Menactra® had been distributed.

In most cases, information regarding seizure workup, including electroencephalogram, head computed tomography and lumbar puncture, drug screen, blood sugar, blood chemistry, and kidney function tests were missing. Patients were 11 to 18 years of age; 8 were males and 4 were females. Six patients developed convulsions or seizure-like activity within a day of vaccination.

Five of these reports occurred in the context of encephalitis or viral encephalitis (n=2), acute disseminated encephalomyelitis (n=2), or viral meningitis (n=1). These cases involved the co administration of at least one other vaccine, were preceded by an upper respiratory illness, or had an alternative infectious etiology.

One case occurred in the context of a vasovagal reaction. It is known that brief seizure-like activity in the context of vasovagal reaction can occur.

In two cases, a diagnosis of epilepsy was considered by the investigators while a nocturnal seizure diagnosis was considered by the neurologist in a third case. Nocturnal seizures are a distinct subset of epilepsy, their mechanisms are poorly understood, and a large number of normal or abnormal sleep phenomena can be confused with seizures. One of these cases involved the co administration of several vaccines and the patient had a prior history of seizure at 10 years of age.

In one case, with a time to onset of 5 days post-vaccination, the findings from the electroencephalogram were reported to be suggestive of an underlying predisposition to seizures.

A point of further consideration was the positive family history for seizures and the subsequent episode of seizure following H1N1 vaccine administration. The latter involved a diagnosis of seizures with sub therapeutic phenytoin levels.

Insufficient information in the two remaining cases precludes a complete assessment and both cases involved the co administration of at least one other vaccine.

Further details on these 12 cases are available in PSUR17 and PSUR18.

No safety concerns have been identified from the review of these additional cases. These cases do not change the prior conclusion of the cumulative review included in the initial submission.

Convulsions remain a very rare occurrence considering the number of vaccine doses that have been distributed.

The available data do not allow a definitive characterization of the relationship between Menactra® and this event when it occurs outside the context of vasovagal syncope.

**Q: Would it be possible to have an update on the incidence of neurological events such as Guillain-Barré or other demyelinating conditions, from further collection of data throughout 2009/2010?**

***Sponsor Response:***

The sponsor refers to the PSUR17 and PSUR18 for an update on the adverse events of GBS and other demyelinating neurological conditions. Both reports include data received between 14 January 2009 and 13 January 2010, and 14 January 2010 and 13 January 2011, respectively. Importantly, during this additional 2-year time period, two large observational studies ("Risk of Guillain-Barré Syndrome Following Meningococcal Conjugate Vaccination" conducted by Harvard Medical School/Harvard Pilgrim Health Care Institute); and Rapid Cycle Analysis conducted by the Vaccine Safety Datalink (VSD) project[36]) did not find an increased risk of GBS associated with Menactra vaccine administration.

Additionally, consistent with the overall decrease in both the number of cases received at Sanofi Pasteur and the reporting rate of AEs during the period covered by the latest PSUR18, the reporting rate of neurological AEs has also decreased as well as the proportion of serious cases belonging to the MedDRA System Organ Class (SOC) Nervous system disorders. Limitations of the safety database for Menactra vaccine include a potential for stimulated reporting of serious neurological conditions following the safety communication alerts made by the FDA and CDC on 30 September 2005 and 20 October 2006, the three MMWR communications from October 2005, April 2006 and October 2006 respectively, and a Sanofi Pasteur "Dear Doctor letter" dated 03 October 2005 regarding the possible association of GBS with Menactra vaccine administration. These communications requested that providers or other persons with knowledge of possible cases of GBS or other clinically significant AEs occurring after vaccination with Menactra vaccine report them to VAERS.

Adverse event reporting rates, however, will typically experience a marked decrease after an initial period of relative hyper-vigilance with regard to the reporting of potential safety concerns following newly marketed vaccines. This effect is known as the Weber Effect. With regard to Menactra vaccine, which has now been in use in the US for over six years, reporting rates have gradually declined. In addition to decreased reporting over time, Menactra vaccine has also been the subject of active surveillance in the form of a large scale epidemiological study conducted by the Department of Population Medicine at Harvard Medical School/Harvard Pilgrim Health Care Institute as well as an active

[36] In 2005, the Vaccine Safety Datalink (VSD) Project team launched an active surveillance system called Rapid Cycle Analysis (RCA). Its goal is to monitor adverse events following vaccination (possible side effects) in near real time, so the public can be informed quickly of possible risks.

sequential safety surveillance (or Rapid Cycle Analysis) conducted by the Vaccine Safety Datalink (VSD) project, a collaborative effort between CDC's Immunization Safety Office and several managed care organizations. Both of these activities may account for further decline in reporting due to the absence of any safety issues revealed by the research. Indeed, the results of these activities have been widely reported in the public domain, in particular, by the ACIP (June, 2010). Vaccine safety endorsements, such as those given by the ACIP, have the likely effect of further reducing AE reporting rates in products that have been shown to possess positive benefit-risk ratio and safety profile.

**Q: Are there any epidemiological postmarketing data to support the clinical efficacy of Menactra?**

***Sponsor Response:***

The efficacy of Menactra vaccine was inferred by demonstrating non-inferiority to the US licensed Meningococcal Polysaccharide Vaccine, Groups A, C, Y and W-135 Combined (Menomune®-A/C/Y/W-135). Post marketing evaluation of the effectiveness in 11 through 18 year old US adolescents was assessed by the US Centers for Disease Control (CDC) and the data have recently been published [37].

## Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended approval of Menactra for the indication:

*for active immunisation of individuals 2 through 55 years of age for the prevention of invasive meningococcal disease caused by N. meningitidis serogroups A, C, Y and W-135.*

The ACPM, taking into account the submitted evidence of pharmaceutical quality, favourable safety profile and immunogenicity (as a surrogate for efficacy), considered there is a favourable benefit-risk profile for this product.

In making this recommendation, the ACPM noted that meningococcal diseases in Australia are caused currently by serogroups B and C with few cases caused by serogroups A, W-135 and Y.

The ACPM agreed with the Delegate that a potential population would be travellers but there was a concern that only one interaction study with other commonly used travel vaccines was submitted.

The specific conditions of registration should include:
Continued robust safety monitoring systems in view of ongoing reports of Guillain- Barré Syndrome, and other neurological disorders associated with the use of the vaccine.

## Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Menactra, Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine, for IM administration, indicated for:

[37] MacNeil *et al.* (2011). Early Estimate of the Effectiveness of Quadrivalent Meningococcal Conjugate Vaccine. *Pediatr Infect Dis J* 30:451-455.

*Active immunisation of individuals 2 through 55 years of age for the prevention of invasive meningococcal disease caused by N meningitides serogroups A, C, Y and W-135.*

*Menactra vaccine is not indicated for the prevention of meningitis caused by other microorganisms or for the prevention of invasive meningococcal disease caused by N meningitides serogroup B.*

*Menactra vaccine is not indicated for treatment of meningococcal infections.*

*Menactra vaccine is not indicated for immunisation against diphtheria.*

# Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

# AUSTRALIAN PRODUCT INFORMATION

## NAME OF THE MEDICINE

Menactra®

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

## DESCRIPTION

Each 0.5 mL dose of vaccine contains:

**Active ingredients:**

- Meningococcal polysaccharide* Group A 4.0 µg/dose
- Meningococcal polysaccharide* Group C 4.0 µg/dose
- Meningococcal polysaccharide* Group Y 4.0 µg/dose
- Meningococcal polysaccharide* Group W-135 4.0 µg/dose
- Diphtheria toxoid protein Approximately 48 µg/dose

* Each of the four polysaccharides is conjugated to diphtheria toxoid.

**Excipients:**

- Sodium chloride 4.35 mg

(within 0.85% Physiological Saline† and 0.5M Phosphate Buffered Saline§, pH 6.8)

- Sodium phosphate – dibasic anhydrous 0.348 mg

(within 0.5M Phosphate Buffered Saline§, pH 6.8)

- Sodium phosphate – monobasic 0.352 mg

(within 0.5M Phosphate Buffered Saline§, pH 6.8)

† 0.85% Physiological Saline is composed of sodium chloride in Water for Injections.

§ 0.5M Phosphate Buffered Saline is composed of sodium chloride, sodium phosphate dibasic anhydrous and sodium phosphate monobasic in Water for Injections.

Menactra vaccine is a sterile, clear to slightly turbid solution of *Neisseria meningitidis* purified capsular polysaccharides of groups A, C, Y and W-135, individually conjugated to a carrier protein. The protein is a purified *Corynebacterium diphtheriae* toxoid, *formalin-detoxified*. Each

0.5 mL dose of vaccine is formulated in sodium phosphate buffered isotonic sodium chloride solution. No preservative or adjuvant is added.

# PHARMACOLOGY

## Mechanism of action

The presence of bactericidal anti-capsular meningococcal antibodies has been associated with protection from invasive meningococcal disease. Menactra vaccine induces the production of bactericidal antibodies specific to the capsular polysaccharides of serogroups A, C, Y and W-135.

# CLINICAL TRIALS

## Immunogenicity

Vaccine efficacy was inferred from the demonstration of immunologic equivalence to a meningococcal polysaccharide vaccine, Menomune®–A/C/Y/W-135, Meningococcal Polysaccharide Vaccine, Groups A, C, Y and W-135 Combined as assessed by Serum Bactericidal Assay (SBA). The SBA used to test sera contained an exogenous complement source that was either human (SBA-H) or, when correlated to SBA-H, baby rabbit (SBA-BR).

The response to vaccination in children 2–10 years old was evaluated by the proportion of subjects having an SBA-H antibody titre of 1:8 or greater, for each serogroup. In adolescents and adults, the response to vaccination was evaluated by the proportion of subjects with a 4-fold or greater increase in bactericidal antibody to each serogroup as measured by SBA-BR.

Immunogenicity was evaluated in three comparative, randomised, US, multi-centre, active controlled clinical trials that enrolled children (2–10 years old), adolescents (11–18 years old), and adults (18–55 years old). Participants received a dose of Menactra vaccine (N=2526) or Menomune–A/C/Y/W-135 vaccine (N=2317). For all age groups studied, sera were obtained before and approximately 28 days after vaccination.

In each of the trials, there were no substantive differences in demographic characteristics between the vaccine groups, between immunogenicity subsets or the overall study population.

## Immunogenicity in Children

Of 1408 enrolled children 2–10 years old, immune responses evaluated in a subset of Menactra vaccine participants (2–3 years old, n=52; 4–10 years old, n=84) and Menomune–A/C/Y/W-135 vaccine participants (2–3 years old, n=53; 4–10 years old, n=84) were comparable for all four serogroups (**Table 1** and **Table 2**).

**Table 1: Comparison of Bactericidal Antibody Responses* to Menactra vaccine and Menomune–A/C/Y/W-135 vaccine 28 Days After Vaccination for a Subset of Participants Aged 2–3 Years**

| | | Menactra vaccine N‡=48-52 | | Menomune–A/C/Y/W-135 vaccine N‡=50-53 | |
|---|---|---|---|---|---|
| **Serogroup** | | | (95% CI)§ | | (95% CI)§ |
| A | % ≥ 1:8† | 73 | (59, 84) | 64 | (50, 77) |
| | GMT | 10 | (8, 13) | 10 | (7, 12) |
| C | % ≥ 1:8† | 63 | (48, 76) | 38 | (25, 53) |
| | GMT | 27 | (14, 52) | 11 | (5, 21) |
| Y | % ≥ 1:8† | 88 | (75, 95) | 73 | (59, 84) |
| | GMT | 51 | (31, 84) | 18 | (11, 27) |
| W-135 | % ≥ 1:8† | 63 | (47, 76) | 33 | (20, 47) |
| | GMT | 15 | (9, 25) | 5 | (3, 6) |

* Serum Bactericidal Assay with an exogenous human complement (SBA-H) source.

† The proportion of participants achieving at least an SBA-H titre of 1:8 was assessed using a 10% non-inferiority margin and a one-sided Type I error rate of 0.025.

‡ N = Number of subset participants with at least one valid serology result at Day 0 and Day 28.

§ The 95% CI for the Geometric Mean Titre (GMT) was calculated based on an approximation to the normal distribution.

**Table 2: Comparison of Bactericidal Antibody Responses* to Menactra vaccine and Menomune–A/C/Y/W-135 vaccine 28 Days After Vaccination for a subset of Participants Aged 4–10 Years**

| | | Menactra vaccine N‡=84 | | Menomune–A/C/Y/W-135 vaccine N‡=84 | |
|---|---|---|---|---|---|
| **Serogroup** | | | (95% CI)§ | | (95% CI)§ |
| **A** | % ≥ 1:8† | 81 | (71, 89) | 55 | (44, 66) |
| | GMT | 19 | (14, 26) | 7 | (6, 9) |
| **C** | % ≥ 1:8† | 79 | (68, 87) | 48 | (37, 59) |
| | GMT | 28 | (19, 41) | 12 | (7, 18) |
| **Y** | % ≥ 1:8† | 99 | (94, 100) | 92 | (84, 97) |
| | GMT | 99 | (75, 132) | 46 | (33, 66) |
| **W-135** | % ≥ 1:8† | 85 | (75, 92) | 79 | (68, 87) |
| | GMT | 24 | (18, 33) | 20 | (14, 27) |

* Serum Bactericidal Assay with an exogenous human complement (SBA-H) source.

† The proportion of participants achieving at least an SBA-H titre of 1:8 was assessed using a 10% non-inferiority margin and a one-sided Type I error rate of 0.025.

‡ N = Number of subset participants with at least one valid serology result at Day 0 and Day 28.

§ The 95% CI for the Geometric Mean Titre (GMT) was calculated based on an approximation to the normal distribution.

In the subset of participants 2–3 years of age with undetectable pre-vaccination titres (i.e., < 4 at Day 0), seroconversion rates (defined as ≥ 8 at Day 28) were similar between the Menactra vaccine and Menomune–A/C/Y/W-135 vaccine recipients. Menactra vaccine participants achieved seroconversion rates of: 57%, serogroup A (n=12/21); 62%, serogroup C (n=29/47); 84%, serogroup Y (n=26/31); 53%, serogroup W-135 (n=20/38). The seroconversion rates for Menomune–A/C/Y/W-135 vaccine recipients were 55%, serogroup A (n=16/29); 30%, serogroup C (n=13/43); 57%, serogroup Y (n=17/30); 26%, serogroup W-135 (n=11/43).

In the subset of participants 4–10 years of age, percentages of participants that achieved seroconversion were similar between the Menactra vaccine and Menomune–A/C/Y/W-135 vaccine recipients. Menactra vaccine participants achieved seroconversion rates of: 69%, serogroup A (n=11/16); 81%, serogroup C (n=50/62); 98%, serogroup Y (n=45/46); 69%, serogroup W-135 (n=27/39). The seroconversion rates for Menomune–A/C/Y/W-135 vaccine recipients were 48%, serogroup A (n=10/21); 38%, serogroup C (n=19/50); 84%, serogroup Y (n=38/45); 68%, serogroup W-135 (n=26/38).

## Immunogenicity in Adolescents

Results from the comparative clinical trial conducted in 881 adolescents aged 11–18 years showed that the immune responses to Menactra vaccine and Menomune–A/C/Y/W-135 vaccine were similar for all four serogroups (**Table 3**).

**Table 3: Comparison of Bactericidal Antibody Responses* to Menactra Vaccine and Menomune–A/C/Y/W-135 Vaccine 28 Days after Vaccination for Participants Aged 11–18 Years**

| | | Menactra vaccine N‡=423 | | Menomune–A/C/Y/W-135 vaccine N‡=423 | |
|---|---|---|---|---|---|
| **Serogroup** | | | (95% CI)§ | | (95% CI)§ |
| **A** | % ≥ 4-fold rise† | 92.7 | (89.8, 95.0) | 92.4 | (89.5, 94.8) |
| | GMT | 5483 | (4920, 6111) | 3246 | (2910, 3620) |
| **C** | % ≥ 4-fold rise† | 91.7 | (88.7, 94.2) | 88.7 | (85.2, 91.5) |
| | GMT | 1924 | (1662, 2228) | 1639 | (1406, 1911) |
| **Y** | % ≥ 4-fold rise† | 81.8 | (77.8, 85.4) | 80.1 | (76.0, 83.8) |
| | GMT | 1322 | (1162, 1505) | 1228 | (1088, 1386) |
| **W-135** | % ≥ 4-fold rise† | 96.7 | (94.5, 98.2) | 95.3 | (92.8, 97.1) |
| | GMT | 1407 | (1232, 1607) | 1545 | (1384, 1725) |

* Serum Bactericidal Assay with baby rabbit complement (SBA-BR).

† Menactra vaccine was non-inferior to Menomune–A/C/Y/W-135 vaccine. Non-inferiority was assessed by the proportion of participants with a 4-fold or greater rise in SBA-BR titre for *N meningitidis* serogroups A, C, Y and W-135 using a 10% non-inferiority margin and a one-sided Type I error rate of 0.05.

‡ N = Number of participants with valid serology results at Day 0 and Day 28.

§ The 95% CI for the Geometric Mean Titre (GMT) was calculated based on an approximation to the normal distribution.

In participants with undetectable pre-vaccination titres (i.e., less than 8 at Day 0), seroconversion rates (defined as a ≥ 4-fold rise in Day 28 SBA titres) were similar between the Menactra vaccine and Menomune–A/C/Y/W-135 vaccine recipients. Menactra vaccine participants achieved seroconversion rates of: 100%, serogroup A (n=81/81); 99%, serogroup C (n=153/155); 98%, serogroup Y (n=60/61); 99%, serogroup W-135 (n=161/164). The seroconversion rates for Menomune–A/C/Y/W-135 vaccine recipients were 100%, serogroup A (n=93/93); 99%, serogroup C (n=151/152); 100%, serogroup Y (n=47/47); 99%, serogroup W-135 (n=138/139).

## Immunogenicity in Adults

Results from the comparative clinical trial conducted in 2554 adults aged 18–55 years showed that the immune responses to Menactra vaccine and Menomune–A/C/Y/W-135 vaccine were similar for all four serogroups (**Table 4**).

**Table 4: Comparison of Bactericidal Antibody Responses* to Menactra Vaccine and Menomune–A/C/Y/W-135 Vaccine 28 Days After Vaccination for Participants Aged 18–55 Years**

| | | Menactra vaccine N‡=1280 | | Menomune–A/C/Y/W-135 vaccine N‡=1098 | |
|---|---|---|---|---|---|
| **Serogroup** | | | (95% CI)§ | | (95% CI)§ |
| A | % ≥ 4-fold rise† | 80.5 | (78.2, 82.6) | 84.6 | (82.3, 86.7) |
| | GMT | 3897 | (3647, 4164) | 4114 | (3832, 4417) |
| C | % ≥ 4-fold rise† | 88.5 | (86.6, 90.2) | 89.7 | (87.8, 91.4) |
| | GMT | 3231 | (2955, 3533) | 3469 | (3148, 3823) |
| Y | % ≥ 4-fold rise† | 73.5 | (71.0, 75.9) | 79.4 | (76.9, 81.8) |
| | GMT | 1750 | (1597, 1918) | 2449 | (2237, 2680) |
| W-135 | % ≥ 4-fold rise† | 89.4 | (87.6, 91.0) | 94.4 | (92.8, 95.6) |
| | GMT | 1271 | (1172, 1378) | 1871 | (1723, 2032) |

* Serum Bactericidal Assay with baby rabbit complement (SBA-BR).

† Menactra vaccine was non-inferior to Menomune–A/C/Y/W-135 vaccine. Non-inferiority was assessed by the proportion of participants with a 4-fold or greater rise in SBA-BR titre for *N meningitidis* serogroups A, C, Y and W-135 using a 10% non-inferiority margin and a one-sided Type I error rate of 0.05.

‡ N = Number of participants with valid serology results at Day 0 and Day 28.

§ The 95% CI for the GMT was calculated based on an approximation to the normal distribution.

In participants with undetectable pre-vaccination titres (i.e., less than 8 at Day 0), seroconversion rates (defined as a ≥ 4-fold rise in Day 28 SBA titres) were similar between the Menactra vaccine and Menomune–A/C/Y/W-135 vaccine recipients. Menactra vaccine participants achieved seroconversion rates of: 100%, serogroup A (n=156/156); 99%, serogroup C (n=343/345); 91%, serogroup Y (n=253/279); 97%, serogroup W-135 (n=360/373). The seroconversion rates for Menomune–A/C/Y/W-135 vaccine recipients were 99%, serogroup A (n=143/144); 98%, serogroup C (n=297/304); 97%, serogroup Y (n=221/228); 99%, serogroup W-135 (n=325/328).

## Concomitant Vaccine Administration

### Tetanus and Diphtheria

The concomitant use of Menactra vaccine and Tetanus and Diphtheria Toxoids Adsorbed, For Adult Use (Td, manufactured by Sanofi Pasteur Inc) was evaluated in a double-blind, randomised, controlled clinical trial conducted in 1021 participants aged 11–17 years. For meningococcal serogroups C, Y and W-135, the proportion of participants with a 4-fold or greater rise in SBA titre was higher when Menactra vaccine was given concomitantly with Td than when Menactra vaccine was given one month following Td. The clinical relevance of this finding has not been

fully evaluated. No interference was observed in the immune response to the tetanus and diphtheria components following concomitant vaccination.

**Typhoid Vi Polysaccharide Vaccine, Typhim Vi®**

The concomitant use of Menactra vaccine and Typhim Vi vaccine (recommended for certain travellers) was evaluated in a double-blind, randomised, controlled clinical trial conducted in 945 participants aged 18–55 years. The immune response to Menactra vaccine and to Typhim Vi vaccine when given concurrently was comparable to the immune response when Menactra vaccine or Typhim Vi vaccine was given alone.

# INDICATIONS

Menactra vaccine is indicated for active immunisation of individuals 2 through 55 years of age for the prevention of invasive meningococcal disease caused by *N meningitidis* serogroups A, C, Y and W-135.

Menactra vaccine is not indicated for the prevention of meningitis caused by other microorganisms or for the prevention of invasive meningococcal disease caused by *N meningitidis* serogroup B.

Menactra vaccine is not indicated for treatment of meningococcal infections.

Menactra vaccine is not indicated for immunisation against diphtheria.

# CONTRAINDICATIONS

Known hypersensitivity to any component of Menactra vaccine including diphtheria toxoid, or a life-threatening reaction after previous administration of a vaccine containing similar components, are contraindications to vaccine administration.

Known history of Guillain-Barré syndrome (see **PRECAUTIONS** section) is a contraindication to vaccine administration.

Known hypersensitivity to dry natural rubber latex (see **PRECAUTIONS** section) is a contraindication to vaccine administration.

Vaccination must be postponed in case of febrile or acute disease. However a minor febrile or non-febrile illness, such as mild upper respiratory infection, is not usually a reason to postpone immunisation.

# PRECAUTIONS

Menactra vaccine may not protect 100% of individuals.

Guillain-Barré syndrome (GBS) has been reported in temporal relationship following administration of Menactra vaccine. An early evaluation of post-marketing adverse events suggested a potential for an increased risk of GBS following Menactra vaccination. However, a recent multi-site retrospective cohort and nested case control study involving over 12 million adolescents, of whom 1.4 million received Menactra vaccine, found no evidence of increased GBS risk associated with the use of Menactra vaccine. Nonetheless, persons previously diagnosed with GBS should not receive Menactra vaccine. (see **ADVERSE EFFECTS** and **CONTRAINDICATIONS** sections).

Menactra vaccine has been evaluated in about 300 Human Immunodeficiency Virus (HIV)-infected subjects. Menactra vaccine was safe and immunogenic in this population. The immune response to Menactra vaccine administered to other immunosuppressed persons has not been studied.

The stopper of the vial contains dry natural rubber latex, which may cause allergic reactions in latex-sensitive individuals.

Before administration, all appropriate precautions should be taken to prevent adverse reactions. This includes a review of the patient's previous immunisation history, the presence of any contraindications to immunisation, the current health status, and history concerning possible sensitivity to the vaccine, similar vaccine, or to latex.

As a precautionary measure, adrenaline injection (1:1000) and other appropriate agents and equipment must be immediately available in case of anaphylactic or serious allergic reactions.

Special care should be taken to avoid injecting the vaccine subcutaneously since clinical studies have not been conducted to establish safety and efficacy of the vaccine using this route of administration.

## Effects on fertility

There were no effects on the mating performance or fertility of female mice intramuscularly injected with Menactra vaccine (at one fifth of the clinical dose) two weeks prior to mating. The effect of Menactra vaccine on male fertility has not been evaluated (see also Use in Pregnancy).

## Use in Pregnancy (Category B2)

In female mice intramuscularly injected with Menactra vaccine (at one fifth of the clinical dose) two weeks prior to mating and on gestation days 6 and 18, there were no significant toxicological effects in the dams, their foetuses or pups. Adequate human data on the use of Menactra vaccine during pregnancy are not available. The vaccine should be used during pregnancy only when clearly needed, such as during an outbreak or prior to necessary travel to an endemic area, and only following an assessment of the risks and benefits.

Sanofi Pasteur maintains a pregnancy registry to monitor foetal outcomes of pregnant women exposed to Menactra vaccine. Healthcare providers are encouraged to inform sanofi pasteur of any pregnant women who receive Menactra vaccine for their inclusion in the vaccination pregnancy registry by calling 1800 829 468.

### Use in Lactation

There are no human or animal data regarding the use of Menactra vaccine during lactation. The potential benefits to the mother and risks to the infant should be considered before administering Menactra vaccine to a nursing woman.

### Paediatric Use

Safety and effectiveness of Menactra vaccine in children below the age of 2 years have not been established.

### Geriatric Use

Safety and effectiveness of Menactra vaccine in adults older than 55 years have not been established.

### Carcinogenicity

No carcinogenicity studies have been conducted with Menactra vaccine.

### Genotoxicity

No genotoxicity studies have been conducted with Menactra vaccine.

## INTERACTIONS WITH OTHER MEDICINES

For information regarding concomitant administration of Menactra vaccine with other vaccines, see **CLINICAL TRIALS** and **ADVERSE EFFECTS** sections.

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses) may reduce the immune response to vaccines.

## ADVERSE EFFECTS

### Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to vaccine use and for approximating rates of those events.

The safety of Menactra vaccine was evaluated in 8 clinical studies that enrolled 10,057 participants aged 2–55 years who received Menactra vaccine and 5266 participants who received Menomune–A/C/Y/W-135 vaccine. The three primary safety studies were randomised, active-controlled trials that enrolled participants 2–10, 11–18 and 18–55 years of age, respectively.

**Serious Adverse Events in All Safety Studies**

Serious adverse events reported within a 6-month time period following vaccination in children 2–10 years old occurred at a rate of 0.6% following Menactra vaccine and at a rate of 0.7% following Menomune–A/C/Y/W-135 vaccine. Serious adverse events reported within a 6-month time period following vaccination in adolescents and adults occurred at a rate of 1.0% following Menactra vaccine and at a rate of 1.3% following Menomune–A/C/Y/W-135 vaccine.

**Solicited Adverse Events in the Primary Safety Studies**

The most frequently reported solicited local and systemic adverse reactions in children aged 2–10 years (**Table 5**) were injection site pain, irritability, diarrhoea, drowsiness, and anorexia respectively. In adolescents, ages 11-18 years (**Table 6**), and adults, ages 18-55 years (**Table 7**), the most commonly reported were injection site pain, headache and fatigue. Except for redness in adults, local reactions were more frequently reported after Menactra vaccination than after Menomune–A/C/Y/W-135 vaccination.

**Table 5: Percentage of US Participants 2–10 Years of Age Reporting Solicited Adverse Reactions Within 7 Days Following Vaccine Administration**

| | **Menactra vaccine *N=1157** | | | **Menomune–A/C/Y/W-135 vaccine *N=1027** | | |
|---|---|---|---|---|---|---|
| **Reaction** | **Any** | **Moderate** | **Severe** | **Any** | **Moderate** | **Severe** |
| Redness† | 21.8 | 4.6 | 3.9 | 7.9 | 0.5 | 0.0 |
| Swelling† | 17.4 | 3.9 | 1.9 | 2.8 | 0.3 | 0.0 |
| Induration† | 18.9 | 3.4 | 1.4 | 4.2 | 0.6 | 0.0 |
| Pain‡ | 45.0 | 4.9 | 0.3 | 26.1 | 2.5 | 0.0 |
| Drowsiness§ | 10.8 | 2.7 | 0.3 | 11.2 | 2.5 | 0.5 |
| Irritability‖ | 12.4 | 3.0 | 0.3 | 12.2 | 2.6 | 0.6 |
| Arthralgia¶ | 6.8 | 0.5 | 0.2 | 5.3 | 0.7 | 0.0 |
| Diarrhoea# | 11.1 | 2.1 | 0.2 | 11.8 | 2.5 | 0.3 |
| Anorexia** | 8.2 | 1.7 | 0.4 | 8.7 | 1.3 | 0.8 |
| Fever†† | 5.2 | 1.7 | 0.3 | 5.2 | 1.7 | 0.2 |
| Vomiting‡‡ | 3.0 | 0.7 | 0.3 | 2.7 | 0.7 | 0.6 |
| Rash§§ | 3.4 | | | 3.0 | | |
| Seizure§§ | 0.0 | | | 0.0 | | |

* N = The total number of subjects reporting at least one solicited reaction. The median age of participants was 6 years in both vaccine groups.

† Moderate: 1.0-2.0 inches, Severe: >2.0 inches.

‡ Moderate: interferes with normal activities, Severe: disabling, unwilling to move arm.

§ Moderate: interferes with normal activities, Severe: disabling, unwilling to engage in play or interact with others.

‖ Moderate: 1-3 hours duration, Severe: >3 hours duration.

¶ Moderate: Decreased range of motion due to pain or discomfort, Severe: unable to move major joints due to pain.

# Moderate: 3-4 episodes, Severe: ≥ 5 episodes.

** Moderate: Skipped 2 meals, Severe: skipped ≥ 3 meals.

†† Oral equivalent temperature; Moderate: 38.4-39.4ºC, Severe: ≥ 39.5ºC.

‡‡ Moderate: 2 episodes, Severe: ≥3 episodes.

§§ These solicited adverse events were reported as present or absent only.

## Table 6: Percentage of Participants 11–18 Years of Age Reporting Solicited Adverse Reactions Within 7 Days Following Vaccine Administration

| | **Menactra vaccine N*=2264** | | | **Menomune–A/C/Y/W-135 vaccine N*=970** | | |
|---|---|---|---|---|---|---|
| **Reaction** | **Any** | **Moderate** | **Severe** | **Any** | **Moderate** | **Severe** |
| Redness‡ | 10.9† | 1.6† | 0.6† | 5.7 | 0.4 | 0.0 |
| Swelling‡ | 10.8† | 1.9† | 0.5† | 3.6 | 0.3 | 0.0 |
| Induration‡ | 15.7† | 2.5† | 0.3 | 5.2 | 0.5 | 0.0 |
| Pain§ | 59.2† | 12.8† | 0.3 | 28.7 | 2.6 | 0.0 |
| Headache‖ | 35.6† | 9.6† | 1.1 | 29.3 | 6.5 | 0.4 |
| Fatigue‖ | 30.0† | 7.5 | 1.1† | 25.1 | 6.2 | 0.2 |
| Malaise‖ | 21.9† | 5.8† | 1.1 | 16.8 | 3.4 | 0.4 |
| Arthralgia‖ | 17.4† | 3.6† | 0.4 | 10.2 | 2.1 | 0.1 |
| Diarrhoea¶ | 12.0 | 1.6 | 0.3 | 10.2 | 1.3 | 0.0 |
| Anorexia# | 10.7† | 2.0 | 0.3 | 7.7 | 1.1 | 0.2 |
| Chills‖ | 7.0† | 1.7† | 0.2 | 3.5 | 0.4 | 0.1 |
| Fever** | 5.1† | 0.6 | 0.0 | 3.0 | 0.3 | 0.1 |
| Vomiting†† | 1.9 | 0.4 | 0.3 | 1.4 | 0.5 | 0.3 |
| Rash‡‡ | 1.6 | | | 1.4 | | |
| Seizure‡‡ | 0.0 | | | 0.0 | | |

* N = The number of subjects with available data.

† Denotes $\rho < 0.05$ level of significance. The *p* values were calculated for each category and severity using Chi Square test.

‡ Moderate: 1.0-2.0 inches, Severe: >2.0 inches.

§ Moderate: Interferes with or limits usual arm movement, Severe: Disabling, unable to move arm.

‖ Moderate: Interferes with normal activities, Severe: Requiring bed rest.
¶ Moderate: 3-4 episodes, Severe: ≥ 5 episodes.
# Moderate: Skipped 2 meals, Severe: Skipped ≥ 3 meals.
** Oral equivalent temperature; Moderate: 38.5-39.4ºC, Severe: ≥ 39.5ºC.
†† Moderate: 2 episodes, Severe: ≥ 3 episodes.
‡‡ These solicited adverse events were reported as present or absent only.

## Table 7: Percentage of Participants 18–55 Years of Age Reporting Solicited Adverse Reactions Within 7 Days Following Vaccine Administration

| | **Menactra vaccine N*=1371** | | | **Menomune–A/C/Y/W-135 vaccine N*=1159** | | |
|---|---|---|---|---|---|---|
| **Reaction** | **Any** | **Moderate** | **Severe** | **Any** | **Moderate** | **Severe** |
| Redness‡ | 14.4 | 2.9 | 1.1† | 16.0 | 1.9 | 0.1 |
| Swelling‡ | 12.6† | 2.3† | 0.9† | 7.6 | 0.7 | 0.0 |
| Induration‡ | 17.1† | 3.4† | 0.7† | 11.0 | 1.0 | 0.0 |
| Pain§ | 53.9† | 11.3† | 0.2 | 48.1 | 3.3 | 0.1 |
| Headache‖ | 41.4 | 10.1 | 1.2 | 41.8 | 8.9 | 0.9 |
| Fatigue‖ | 34.7 | 8.3 | 0.9 | 32.3 | 6.6 | 0.4 |
| Malaise‖ | 23.6 | 6.6† | 1.1 | 22.3 | 4.7 | 0.9 |
| Arthralgia‖ | 19.8† | 4.7† | 0.3 | 16.0 | 2.6 | 0.1 |
| Diarrhoea¶ | 16.0 | 2.6 | 0.4 | 14.0 | 2.9 | 0.3 |
| Anorexia# | 11.8 | 2.3 | 0.4 | 9.9 | 1.6 | 0.4 |
| Chills‖ | 9.7† | 2.1† | 0.6† | 5.6 | 1.0 | 0.0 |
| Fever** | 1.5† | 0.3 | 0.0 | 0.5 | 0.1 | 0.0 |
| Vomiting†† | 2.3 | 0.4 | 0.2 | 1.5 | 0.2 | 0.4 |
| Rash‡‡ | 1.4 | | | 0.8 | | |
| Seizure‡‡ | 0.0 | | | 0.0 | | |

* N = The number of subjects with available data.
† Denotes $\rho < 0.05$ level of significance. The *p* values were calculated for each category and severity using Chi Square test.
‡ Moderate: 1.0-2.0 inches, Severe: >2.0 inches.
§ Moderate: Interferes with or limits usual arm movement,, Severe: Disabling, unable to move arm.
‖ Moderate: Interferes with normal activities, Severe: Requiring bed rest.
¶ Moderate: 3-4 episodes, Severe: ≥ 5 episodes.
# Moderate: Skipped 2 meals, Severe: Skipped ≥ 3 meals.
** Oral equivalent temperature; Moderate: 39.0-39.9ºC, Severe: ≥40.0ºC.
†† Moderate: 2 episodes, Severe: ≥ 3 episodes.
‡‡ These solicited adverse events were reported as present or absent only.

## Adverse Events in Concomitant Vaccine Studies

### Local and Systemic Reactions when Given with Td Vaccine

The two vaccine groups reported similar frequencies of pain, induration, redness and swelling at the Menactra injection site, as well as, at the Td injection site. Pain was the most frequent local reaction reported at both the Menactra and Td injection sites.

The overall rate of systemic adverse events was higher when Menactra and Td vaccines were given concomitantly than when Menactra vaccine was administered 28 days after Td. In both groups, the most common reactions were headache and fatigue.

### Local and Systemic Reactions when Given with Typhim Vi Vaccine

The two vaccine groups reported similar frequencies of pain, induration, redness and swelling at the Menactra injection site, as well as, at the Typhim Vi injection site. Pain was the most frequent local reaction reported at both the Menactra and Typhim Vi injection sites. More participants experienced pain after Typhim Vi vaccination than after Menactra vaccination (76% versus 47%). The majority (70%-77%) of local solicited reactions for both groups at either injection site were reported as mild and resolved within 3 days post-vaccination. In both groups, the most common systemic reaction was headache and fatigue.

## Post-Marketing Reports

Based on spontaneous reporting, the following additional adverse events have been reported during the commercial use of Menactra vaccine. These events have been very rarely reported. However, because these events were reported voluntarily from a population of uncertain size, it is not always possible to reliably calculate their frequency or to establish a causal relationship to Menactra vaccine exposure.

Immune system disorders:

Hypersensitivity reactions such as anaphylactic/anaphylactoid reaction, wheezing, difficulty breathing, upper airway swelling, urticaria, erythema, pruritus, hypotension

Nervous system disorders:

Guillain-Barré syndrome, paraesthesia, vasovagal syncope, dizziness, convulsion, facial palsy, acute disseminated encephalomyelitis, transverse myelitis

Musculoskeletal and connective tissue disorders:

Myalgia

# DOSAGE AND ADMINISTRATION

Menactra vaccine should be administered as a single 0.5 mL injection by the **intramuscular** route, preferably in the deltoid region.

Do not administer this product intravenously, subcutaneously, or intradermally.

The need for, or timing of, a booster dose of Menactra vaccine has not yet been determined.

There are limited data available on the length of time that should lapse before administration of Menactra vaccine in those individuals who have been previously vaccinated with other meningococcal vaccine.

For further information, refer to the current National Immunisation Handbook.

Parenteral drug products should be inspected visually for container integrity, particulate matter and discoloration prior to administration, whenever solution and container permit.

Menactra vaccine must not be mixed with any vaccine in the same syringe. Therefore, separate injection sites and different syringes should be used in case of concomitant administration.

Product is for single use in one patient only. Discard any residue.

## OVERDOSE

No case of overdose has been reported.

## INCOMPATIBILITIES

In the absence of compatibilities studies, this vaccine must not be mixed with other vaccines or medicinal products.

## PRESENTATION AND STORAGE CONDITIONS

**Presentation**

Vial, 1 Dose (5 vials per package)

**Storage**

Store at 2°C to 8°C (Refrigerate. Do not freeze). Product that has been exposed to freezing should not be used. Do not use after expiration date.

Protect from light.

## NAME AND ADDRESS OF THE SPONSOR

**Sanofi Pasteur Pty Ltd**

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## POISON SCHEDULE OF THE MEDICINE

S4 Prescription Only Medicine

## DATE OF APPROVAL

20 July 2011

**Therapeutic Goods Administration**

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Reference/Publication #