Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Meningococcal Conjugated Vaccine

Proprietary Product Name: Menveo

Sponsor: Novartis Vaccines and Diagnostics Pty Ltd

September 2010

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.

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I. Introduction to Product Submission

Product Details

Type of Submission	New Chemical Entity
Decision:	Approved
Date of Decision:	20 May 2010
Active ingredient(s):	Meningococcal group A oligosaccharide 10 µg conjugated to *Corynebacterium diphtheriae* CRM_{197} protein 17.7 - 33.3 µg Meningococcal group C oligosaccharide 5 µg conjugated to *Corynebacterium diphtheriae* CRM_{197} protein 7.1 - 12.5 µg Meningococcal group W-135 oligosaccharide 5 µg conjugated to *Corynebacterium diphtheriae* CRM_{197} protein 3.3 – 8.3µg Meningococcal group Y oligosaccharide 5 µg conjugated to *Corynebacterium diphtheriae* CRM_{197} protein 5.6 - 10 µg.
Product Name(s):	Menveo meningococcal conjugate vaccine.
Sponsor's Name and Address:	Novartis Vaccines and Diagnostics Pty Ltd 54 Waterloo Road, North Ryde NSW 2113
Dose form(s):	Powder and solvent solution for injection
Strength(s):	10 µg of MenA oligosaccharide and 5 µg of MenC, MenW & MenY oligosaccharides / 0.5 ml dose
Container(s):	Composite pack: single dose vial and syringe
Pack size(s):	Single dose vial and syringe
Approved Therapeutic use:	Menveo is indicated for active immunisation of adolescents (from 11 years of age) and adults to prevent invasive disease caused by Neisseria meningitidis serogroups A, C, W-135 and Y. The use of this vaccine should be in accordance with official recommendations.
Route(s) of administration:	Intramuscular injection (IM)
Dosage:	0.5 mL dose
ARTG number:	158477

Product Background

The most common meningococcal diseases in Australia are 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.

Two types of meningococcal vaccine are currently available in Australia. One type is the quadrivalent polysaccharide vaccine (such as Menomune), which is indicated for active immunization of adults and children older than 2 years and protects against diseases caused by serogroups A, C, W135 and Y for limited duration of 2 or 3 years. Another type is the monovalent conjugate vaccine against serogroup C (such as Menjugate),which is indicated for use in children as young as 6 weeks of age as well as older children and adults and provides long term protection against serogroup C.

Regulatory Status

Listed below is the Menveo marketing authorization status worldwide.
USA: Submitted on 29 Aug 2008 to FDA. Approved on 19 Feb 2010
Europe: Submitted on 31 Oct 2008 to EMA. Approved by European Commission on 15 March 2010
Canada: Submitted on 18 December 2008 to Health Canada. Approved on 21 May 2010
Switzerland: Submitted on 01 December 2008 to Swissmedic
Argentina: Submitted on 20 Mar 2009. Approved on 02 July 2010
Chile: Submitted on 21 Apr 2009. Approved on 31 May 2010
Brazil: Submitted on 27 Jul 2009
Venezuela: Submitted on 28 Sep 2009
Mexico: Submitted on 23 Oct 2009
Turkey: Submitted on 02 Nov 2009 (multi package presentation). Submitted on 02 Dec 2009 (single package presentation)
Indonesia: Submitted on 13 Nov 2009. Approved on 28 July 2010
Kuwait: Submitted on 24 Nov 2009
Pakistan: Submitted on 10 February 2009. Approved on 09 July 2010
Tunisia: Submitted on 07 June 2010

Product Information

The approved Product Information (PI) document current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

Structure

There are two sets of drug substances in this application. The purified polysaccharides and carrier protein represent one set. The other set being the conjugate molecules consisting of the 4 oligosaccharides separately conjugated to the protein.

The long-chain polysaccharides are isolated from the A, C, W_{135} & Y strains of *Neisseria (N) meningitidis*. The CRM_{197} carrier protein is a non-toxic form of diphtheria toxin purified from a mutant of *Corynebacterium diphtheriae*. 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 four conjugates consist of oligosaccharides derived from *N. meningitidis* serogroups A, C, W & Y covalently bound to CRM_{197}. The approximated structure of each conjugate is:

- MenA-CRM_{197} - The average degree of polymerisation of the oligosaccharide is 12-22, resulting in a molecular weight of around 5000 Da. With about 5 to 6 saccharide moieties linked to the protein, the final molecular weight of the conjugate ranges from 80 to 90 kD.

- MenC-CRM_{197} - The average degree of polymerisation of the oligosaccharide is 16-17, resulting in a molecular weight of around 5000 Da. With about 6 saccharide moieties linked to the protein, the final molecular weight of the conjugate ranges from 85 to 95 kD.
- MenW-CRM_{197} - The average degree of polymerisation of the oligosaccharide is 20, resulting in a molecular weight of around 10000 Da. With about 5 to 7 saccharide moieties linked to the protein, the final molecular weight of the conjugate ranges from 110 to 120 kD.
- MenY-CRM_{197} - The average degree of polymerisation of the oligosaccharide is 20, resulting in a molecular weight of around 10000 Da. With about 4 to 5 saccharide moieties linked to the protein, the final molecular weight of the conjugate is approximately 100 kD.

Manufacture

The four polysaccharides are manufactured by extraction and purification of the polysaccharide from each of four serotypes of *N. meningitidis*. Strains are cultured, inactivated using formaldehyde, and the polysaccharides recovered using a series of purification steps. The CRM_{197} carrier protein is extracted and purified from a non-toxigenic strain of *Corynebacterium diphtheriae*.

The polysaccharides are then hydrolysed and sized into oligosaccharides, before being covalently linked to the CRM197 protein via a linker molecule (bis-N-hydroxysuccinimide ester of adipic acid).

There are no viral safety or transmissible spongiform encephalopathies (TSE) issues, 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 reviewed and found to be satisfactory. Most of the specifications are justified and appropriate validation data have been submitted in support of the test procedures.

Stability

Stability data for the polysaccharide and protein bulks have been generated at -15°C for up to 24 months from the current site of manufacture. This data (to date), and data from the previous manufacturing site show no evidence of instability or degradation. The data submitted support a shelf life of 30 months at -15°C.

Stability data for the conjugate bulks show no evidence of instability or degradation. During the evaluation process, real time stability data was provided to support the 24 month shelf life when stored at -15°C."

Drug Product

Formulation(s)

Menveo is a vaccine containing 10 µg of MenA-CRM_{197} and 5 µg of MenC- CRM_{19}, MenW CRM_{19} & MenY CRM_{197} / 0.5 ml dose. Menveo consists of one vial containing the

lyophilised MenA Conjugate Component plus excipients, and one syringe containing the liquid MenCWY Conjugate Component plus excipients. The reconstituted sterile liquid vaccine is administered by intramuscular injection and contains meningococcal serogroup A, C, W-135 and Y oligosaccharides conjugated individually to *Corynebacterium diphtheriae* CRM197 protein.

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

Menveo is presented as a vial (type I glass) of MenA lyophilised Conjugate Component with a synthetic rubber stopper and a syringe (type I glass) of MenCWY liquid Conjugate Component with a tip cap (type I elastomeric closure with 10 % Dry Natural Rubber: latex).

Manufacture

The lyophilised MenA component contains the MenA-CRM_{197} conjugate, potassium phosphate monobasic (5 mM) and sucrose (12.5 mg/dose) as a stabiliser. The MenCWY component contains the MenC-CRM_{197}, MenW-CRM_{197} & MenY-CRM_{197} conjugates, sodium phosphate - monobasic monohydrate (2.5mM), sodium phosphate - dibasic dihydrate (7.5mM), sodium chloride and water for injections.

Specifications

The proposed specifications, which control identity, potency, purity, dose delivery and other physical, chemical and microbiological properties relevant to the clinical use of the product were reviewed and found to be satisfactory. Most of the specifications are 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. The proposed shelf life is 36 months when stored at 2-8°C. In-use stability data (up to 8 hours at 25°C) have also been submitted.

Bioavailability

Biopharmaceutic data are not required for this product.

Quality Summary and Conclusions

The administrative, chemical, pharmaceutical and microbiological data 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, the Evaluation of Labelling Aspects and the Evaluation of Manufacturing and Quality Control Aspects and were referred to the applicant for comment or resolution. All issues raised were satisfactorily resolved prior to approval was granted for the product.

III. Nonclinical Findings

Introduction

Menveo is a tetravalent meningococcal vaccine designed to provide simultaneous active immunity to four disease-causing serotypes of *N. meningitidis* in adolescents ($\geq$ 11 years of age) and adults. The complete vaccine contains four meningococcal capsular oligosaccharide antigens, all individually conjugated to the non-toxic *Corynebacterium diphtheriae* protein,

CRM_{197}. The meningococcal antigens contained in Menveo are from *N. meningitidis* serogroups A, C, W-135 and Y. The final Menveo® preparation (0.5mL) contains MenA at 10mg (plus CRM_{197} protein at 12.5 to 33.0 mg), MenC at 5 mg with 6.25 to 12.5mg CRM_{197}, and MenW and MenY at 5mg with CRM_{197} at 3.3 to 10 mg. The final vaccine preparation is intended for intramuscular injection.

A number of other meningococcal vaccines are already registered in Australia, namely, the polysaccharide vaccines Mencevax AC, Mencevax ACWY (SmithKline Beecham) and Menomune (Sanofi Pasteur), as well as the monovalent vaccines Menjugate (Novartis, CSL), NeisVacC (Baxter AG) and Meningitec (Wyeth). These are registered for immunisation of adults and children over 2 years of age against the respective *N. meningitidis* group(s), in subjects who are close contacts of patients with the disease, in travellers to countries where the disease is endemic or highly epidemic, and for controlling epidemics in confined communities. According to 2006 data, the most prevalent meningococcal disease serogroup is group B, followed by group C (*Australian Meningococcal Surveillance Network*, 2007).

To encourage antigenicity, each of the four capsular meningococcal oligosaccharides is individually conjugated to the mutant *Corynbacterium diptheriae* protein, CRM_{197}. CRM (Cross-Reactive Material) in its native form is toxic, but the stable point mutation (Δ197: G → A) renders the protein non-toxic. CRM_{197} has been previously presented as a conjugate in another vaccine (for example, Prevenar, Wyeth).

Quality of the dossier: The quality and presentation of the dossier was generally very good, with clear labelling and easy access to comprehensive data. This is particularly true of the rabbit toxicology and rabbit reproductive and developmental studies performed in US-based laboratories. Where individual animal data was presented by treatment group, a group mean would have assisted the data evaluation. The mouse immunogenicity study data, from the same lab in Italy that performed the rabbit serology, was generally adequate.

Nonclinical studies with Menveo vaccine consisted of non-Good Laboratory Practice (GLP) immunogenicity studies in mice, with GLP-compliant toxicity and developmental studies performed in NZ White rabbits. It should be noted that the serum collected from rabbits for antibody analyses were collected under GLP-compliant study conditions.

Pharmacology

Primary pharmacology (Immunogenicity): N. meningitidis is a commensal organism in the nasopharyngeal mucosa of approximately 10% of the human population. Although invasive meningococcus disease is relatively rare, meningococcal septicaemia and meningitis may be fatal, and fatal septicaemia may occur rapidly (van Deuren *et al*, 2000; de Souza & Seguro, 2008; Virgi, 2009)[1]. The capsules of *N. meningitidis* contain polysaccharides (linear homopolymers), the antigens of which consist of repeating epitopes that are not processed by antigen-presenting cells, but interact directly with B cells, inducing antibodies in the absence of T cells that is- they are T-independent (T-I) antigens. In contrast to protein antigens, which are T-dependent, responses to CHO antigens are characterised by their short duration, a dominance of Imunoglobulin M (IgM), poor responses in children less than 2 years of age,

[1] Van Deuren M, Brandtzaeg P and van der Meer, JW. (2000). Update on meningococcal disease with emphasis on pathogenesis and clinical management. *Clinical Microbiology Reviews* 13:144-166.

de Souza AL and Seguro AC. (2008). Two centuries of meningococcal infection: from Vieusseux to the cellular and molecular basis of disease. J Med Microbiol. 57:1313-21.

Virji M. Pathogenic neisseriae: surface modulation, pathogenesis and infection control. *Nat Rev Microbiol.* 2009 Apr;7:274-86.

and a failure to induce immunological memory (Goldblatt, 1998)[2]. The conjugation of a CHO antigen to a protein carrier may change it from a T-independent to a T-dependent antigen, as demonstrated by the successful development of conjugate vaccines against *Haemophilus influenzae* (HibTITER) and other diseases. Previously approved and registered monovalent meningococcal vaccines (for example Meningitec) have utilised this conjugate strategy to encourage T-cell dependent immunity post-vaccination, and Menveo also includes a conjugate format, but in a tetravalent antigen context.

There are at least 12 or 13 serogroups of *N. meningitidis*, defined according to their outer capsular polysaccharides, namely A, B, C, 29E, H, I, K, L, W_{135}, X, Y and Z, with over 90% of cases of meningitis caused by serogroups A, B and C (Peltola, 1998)[3]. With the advent of enhanced genotyping techniques, there are now suggestions that genetic markers be included in meningococcal strain and serogroup classification (Jolley *et al.*, 2007; Corless *et al.*, 2008)[4]. Geographical differences occur in terms of the most prevalent meningococcal disease strain. Multivalent vaccines are being developed to address the variation in meningococcal disease strains, particularly with increased and rapid travel leading to the risk of inadvertent spread between communities. Menveo is an example of such a vaccine.

Mouse - Immunogenicity studies in female BALB/c strain mice (6-8 weeks of age) were conducted where the MenACWY (*Menveo*) vaccine was administered twice (Day 0 and Day 28) with or without an Al^{3+} adjuvant (aluminium hydroxide, $Al(OH)_3$, or aluminium phosphate, $AlPO_4$). The total Men ACWY vaccine was also compared to each of the four Men vaccine antigens alone.

Specific anti-meningococcal antibody responses were detected for all vaccine combinations (monovalent or tetravalent responses) by Enzyme-linked immunosorbent assay (ELISA), and all meningococcal vaccines elicited significant serum bactericidal activity (SBA). No antibody was detected by ELISA or SBA in adjuvant alone controls. In general, antibody responses were best following administration of an $Al(OH)_3$ adjuvanted vaccine, compared to either the $AlPO_4$ adjuvant or non adjuvant vaccines. This was particularly true when examining post vaccine response to individual Men antigens. For tetravalent antibody responses post-MenACWY vaccination, the $Al(OH)_3$ adjuvant was superior for MenA, C and W responses (ELISA), but not MenY. SBA responses were generally equivalent for both adjuvants against MenCWY, but with a $\log_2$ increase for MenA with the $Al(OH)_3$ adjuvant.

Another mouse immunogenicity study examined the comparison of the MenACWY vaccine with and without adjuvant. The adjuvant chosen for this study was $AlPO_4$. By both ELISA and SBA, antibody responses to MenA were enhanced by the presence of the $AlPO_4$ adjuvant. The MenC antibody response showed a stronger ELISA titre with $AlPO_4$, but a slightly stronger SBA without adjuvant. MenW antibody titre as determined by ELISA was stronger without adjuvant, but SBA was enhanced by adjuvant. MenY antibody response

[2] Goldblatt, D (1998). Recent developments in bacterial conjugate vaccines. *Journal of Medical Mirobiology* 47:563-567.

[3] Peltola, H (1998). Meningococcal vaccines: current status and future possibilities. *Drugs* 55:347-366.

[4] Jolley KA, Brehony C and Maiden MC. (2007). Molecular typing of meningococci: recommendations for target choice and nomenclature. *FEMS Microbiol Rev.* 31:89-96.

Corless CE, Kaczmarski E, Borrow R and Guiver M. (2008). Molecular characterization of *N. meningitidis* isolates using a resequencing DNA microarray. *J Mol Diagn.* 10:265-271.

showed equivalent ELISA titres, but enhanced SBA with adjuvant (although it should be noted that the MenACWY vaccine alone stimulated a SBA titre of 1/16384). This study suggests that MenCWY immunogenicity is strong without adjuvant, but given that the MenA response is improved significantly by adjuvant, it is advisable that adjuvant is used routinely for this vaccine. There is a large discrepancy in anti-MenY SBA response between study 244-07 and 245-07, indicating that this antigen may be the most antigenically labile of the four antigens included in this meningococcal vaccine.

$AlPO_4$ adjuvant doses containing 0.030 mg or 0.015 mg elicited weaker antibody responses compared to the 0.060 mg preparation.

Rabbit - Sera were collected from rabbits receiving five intramuscular doses of MenACWY vaccine plus adjuvant, with each vaccination separated by 14 days (first dose on Day 0 and the final dose on Day 56 of the study). Antibody response post vaccination was monitored from Day 14 until Day 70 of the study, two weeks after the final vaccination. For all vaccine groups in this study, with either adjuvant, strong ELISA titres and SBA were detected by Days 28-42 of the study, with persistent antibody detectable two weeks after the final vaccine dose on Day 56.

In terms of ELISA titre and SBA, $Al(OH)_3$ adjuvant stimulated generally stronger responses compared to $AlPO_4$. This was particularly noticeable at Day 14 (only one vaccine dose). The anti-MenY response showed the strongest Day 14 ELISA titre and SBA. Antibody kinetics (ELISA) from Day 14 to Day 70 showed that the MenA response was increasing at Day 70 (2-weeks post final vaccine, both adjuvants), while the responses for MenCWY were strong, but reduced by Day 70 in comparison to Day 42 ($Al(OH)_3$). The antibody kinetics post MenACWY plus $AlPO_4$ showed a reduction in antibody titre to MenW when comparing Day 70 to Day 42, but ELISA titres for MenC and MenY were similar for Days 42 and 70. While $AlPO_4$ may not simulate antibody titres of the same strength as $Al(OH)_3$, this adjuvant may be advantageous in terms of persistence of serum antibody. SBA was generally stronger post MenACWY vaccination with $Al(OH)_3$, on both Days 14 and 42, compared to MenACWY plus $AlPO_4$. This was particularly true for the antibody response to MenY.

Correlation to human protective immunity - In humans immunised with *N. meningitidis* C polysaccharide or conjugate vaccines, serogroup-specific Ig G concentrations were reportedly well correlated with bactericidal titres, and a bactericidal titer of 1/4 was correlated with protection from invasive disease (Goldschneider *et al*, 1969)[5]. An efficacy trial with a meningococcal A polysaccharide vaccine in Finland reported that protective immunoglobulin concentrations against *N. meningitidis* serogroup A appeared to be in the range of 1-2 mg/mL (Peltola *et al*, 1977)[6], and this level has also been presumed to be the protective level against meningococcal serogroup C, based on the similarity of the pathogens.

Conclusion - The Menveo tetravalent MenACWY vaccine elicited detectable antibody responses in both mouse and rabbit, as quantified by ELISA and SBA. The kinetics of antibody response varied depending on the Men antigen and whether adjuvant was adsorbed to the vaccine, but generally appeared to be long term (rabbit study) and to consistently induce serum bactericidal activity greater than a titre of ¼, which according to previous

[5] Goldschneider et al (1969). Human immunity to the meningococcus. I. The role of humoral antibodies. *J. Exp. Med.* 129: 1327-1348.

[6] Peltola, H *et al* (1977). Clinical efficacy of meningococcus group A capsular polysaccharide vaccine in children three months to five years of age. *N. Engl. J. Med.* 297:686-691.

studies on MenC vaccines should correlate with protection from wild meningococcal infection in humans. Therefore, the Menveo meningococcal vaccine is fully immunogenic in the two animal species examined.

Pharmacokinetics

Pharmacokinetic studies were not performed in support of this application. For vaccines, this is not unusual, as pharmacokinetic properties of vaccines do not provide useful information for establishing adequate dosing recommendations.

Relative Exposure

When comparing "dose by body surface area" (BSA - mg/m^2), total antigen exposure was 11.8 fold higher for rabbit compared to human, and 47.1 fold higher for mouse compared to human exposure. These values were calculated against the proposed human Menveo dose described in the product information and supporting literature. For rabbit and human, individual antigen doses are MenA, 10 mg plus MenCWY at 5 mg each. For mouse, the calculations are based on an individual antigen dose of 2.0 mg for all four Men antigens. The calculations supporting this interpretation are located in the following table.

Table 1 - Calculation and comparison of relative tetravalent meningococcal total antigen exposure for human, rabbit and mouse.

Species (Study)	Weight (kg)	Vaccine Dose* (mg)	Vaccine Dose (mg)	Vaccine Dose (mg/kg)	Dose by Body Surface Area (BSA - mg/m^2)
Human *(Proposed human dose)*	50	25	0.025	0.0005	0.017
Rabbit *(Toxicology study 02-2752)*	3.0	40	0.040	0.013	0.200
Mouse *(Immunogenicity studies 244-07 + 245-07)*	0.03	8	0.008	0.267	0.801

* Total meningococcal antigen dose per vaccine application, comprising MenA, C, W-135 and Y.

For rabbit and human, vaccine is administered in a 0.5 mL volume intramuscularly.

Toxicology

Both repeat and single dose toxicity studies were conducted in NZ White rabbits. Apart from local inflammation at the site of vaccine injection, the single dose study revealed no toxicity in vaccinated rabbits. A total of four rabbits were used in this study, with two sacrificed at Day 2 of the study and the remaining two rabbits sacrificed at Day 14. Given these small numbers, it was not possible to derive meaningful statistical conclusions to assist in the interpretation of single dose study data. This was particularly so for body weight and food consumption data where an unusual response by one rabbit can skew the group mean for these parameters. Group sizes are recommended as comprising three or more individuals to assist with statistical analysis and subsequent interpretation.

For the repeat dose study (a total of five vaccine doses over 70 days), in general no significant vaccine effect (compared to adjuvant alone controls) was noted for heart rate, eye condition and function, body temperature, food consumption, body weight gain and organ weights. A small body temperature spike was noted in female rabbits two days after the final vaccine dose (Day 58; both adjuvants) and thymus weight was significantly reduced for MenACWY + $AlPO_4$ vaccinated female rabbits compared to $AlPO_4$ alone controls (terminal sacrifice). This was not observed for MenACWY + $Al(OH)_3$ vaccinated female rabbits. Some minor food consumption differences were noted, but were not consistently associated with vaccinated groups and were likely due simply to natural variation. For clinical laboratory indices a number of haematological, clinical chemistry and blood coagulation parameters were altered significantly (at $p \leq 0.001$ or $p \leq 0.05$) when comparing adjuvant alone control groups with MenACWY-vaccinated groups, but these generally were not consistent and therefore of no concern. However, a consistent and significant reduction of eosinophil and basophil numbers were observed for MenACWY-vaccinated male and female rabbits (both adjuvants); for male vaccine plus $Al(OH)_3$ animals this was accompanied by a significant reduction in total white blood cell (WBC) numbers compared to $Al(OH)_3$ controls. Since the reductions in eosinophil and basophil numbers were not consistently associated with an overall reduction in white cell number, there can be the reasonable suggestion that this meningococcal vaccine alters eosinophil/basophil activity. The *PorB* surface protein of *N. meningititis* has been associated with an eosinophilic "recall" response (Burke *et al*., 2007)[7] and a very rare case of eosinophilic myocarditis has been associated with meningococcal C vaccination in a 14 year old child (Barton *et al*., 2008)[8].

CRM197 toxicity - Previously evaluated toxicity studies of registered and proposed vaccines containing non-meningococcal polysaccharides conjugated to CRM_{197} protein, and previously evaluated toxicity data for CRM_{197} protein, raised no toxicological concerns.

Secondary pharmacology: No studies were submitted with this application and this is considered acceptable as there are no new components in the final formulation compared with currently marketed vaccines.

Local tolerance: Predictable inflammation around the site of intramuscular injection was noted histologically, with discolouration and "redness" noted frequently on the macroscopic examination of the injection site for vaccine (± adjuvant) and control rabbits. Oedema and haematoma were noted, but for only two cases so these were considered rare and not problematic.

Carcinogenicity and genotoxicity: No carcinogenicity or genotoxicity studies were submitted for this study, and they are not required for a conventional vaccine such as Menveo (European Medicines Evaluation Agency (EMEA) guidance document CPMP/SWP/465/95).

Assessment of reproductive and embryonic toxicity: Female rabbits were vaccinated following a similar protocol as described above for the rabbit toxicity studies, receiving a

[7] Burke JM, Ganley-Leal LM, Khatri A and Wetzler LM. (2007). Neisseria meningitidis PorB, a TLR2 ligand, induces an antigen-specific eosinophil recall response: potential adjuvant for helminth vaccines? *J Immunol.*,179:3222-3230.

[8] Barton M, Finkelstein Y, Opavsky MA, Ito S, Ho T, Ford-Jones LE, Taylor G, Benson L and Gold R. (2008). Eosinophilic myocarditis temporally associated with conjugate meningococcal C and hepatitis B vaccines in children. *Pediatr Infect Dis J.*, 27:831-835.

total of five doses over the course of the study. Virgin rabbits were randomised into eight separate groups comprising saline alone and $AlPO_4$ alone control groups, two vaccine (± aluminium adjuvant) groups specifically for antibody studies, and the remaining groups for maternal and foetal toxicology study, following varying MenACWY vaccine dose regimens.

The MenACWY vaccine total antigen dose for the above-described toxicity study was 40 mg (0.5 mL), whereas for these reproductive/developmental studies, either 25 mg or 50 mg MenACWY total antigen doses were used at individual vaccination time points. The vaccination regime included three vaccine doses prior to mating at 25 mg (in 0.5 mL) MenACWY (mating occurred on Day 35 of the study), with two additional vaccine doses delivered after mating in the "presumed gestation" phase of the study (Days 7 and 20 of gestation). The two presumed gestation vaccine doses were either 25 mg in 0.5 mL or 50 mg in 1.0 mL, with or without the aluminium adjuvant. The timing and frequency of vaccine delivery prior to pregnancy was designed to ensure significant maternal and fetal antibody titres during foetal organogenesis, with the subsequent two doses during presumed gestation required to ensure persistent and high antibody titre during foetal development.

Significant antibody, as detected by ELISA and SBA, was detected in maternal and foetal serum samples from MenACWY (± aluminium adjuvant) vaccinated groups. Antibody responses to all Men vaccine antigens were detected in these groups.

Maternal rabbits - By Day 31 (4 days prior to mating), SBA was detected for all Men vaccine antigens at titres of > 32 - < 256 in rabbits vaccinated with MenACWY alone. For MenACWY plus aluminium adjuvant vaccinated female rabbits at Day 31 (pre-mating), SBA responses were stronger, with titres ranging from > 64 - < 1024. Total antibody titres as measured by ELISA were correspondingly enhanced for rabbits vaccinated with MenACWY plus aluminium adjuvant. ELISA and SBA titres were also assessed during the presumed gestation phase of the study. At Day 29 post-mating, ELISA titres were increased for all Men antigens, particularly MenY, following MenACWY (alone) vaccination. In spite of the enhanced ELISA titre, SBA for MenY remained at > 64 - < 128, compared to the pre-mating titre post MenACWY alone vaccination. Post MenACWY alone SBA was increased for MenA, MenC and MenW at Day 29 of the gestational phase. For MenACWY plus aluminium vaccinated female rabbits, SBA was increased for Men A, C and W, but not MenY at Day 29 of the gestational phase. Compared to the Day 31 pre-mating ELISA titres, total anti-Men antibody was increased by Day 29 of the gestation phase, particularly for MenA and MenY.

In summary, following multiple intramuscular vaccinations with either MenACWY alone, or MenACWY adsorbed to aluminium ($AlPO_4$) adjuvant, significant and persistent anti-MenA, MenC, MenW and MenY antibody titres were detected by ELISA and SBA during both the pre-mating and presumed gestational phase of the study. The presence of aluminium adjuvant generally enhanced the antibody response in maternal rabbits.

Rabbit fetuses - Maternal humoral immunity was successfully transferred to fetuses by the completion of the study, as measured by both ELISA and SBA, for all vaccine (± aluminium) groups. Serum samples for fetal antibody analysis were collected from all eight groups included in the study, not just groups IV and VIII.

The saline alone (Group I) and adjuvant alone (Group V) had ELISA and SBA titres less than four (< 4) and were therefore classified as "non-responders". Significant ELISA and SBA titres were found for fetuses from rabbits vaccinated with MenACWY alone, and increasing the vaccine antigen dose to 50 mg in the presumed gestation phase of the maternal rabbits did not enhance either SBA or ELISA titres in fetuses. For the fetuses from MenACWY plus aluminium adjuvant vaccinated maternal rabbits, the augmented presumed gestational dose of

50 mg vaccine antigen did result in a higher SBA and ELISA endpoints (when considering MenA, C, W, Y collectively) compared to the group vaccinated with 25 mg. The presence of aluminium adjuvant did enhance ELISA and SBA titres in fetuses, reflecting the generally stronger humoral immune response induced in the vaccinated maternal rabbits.

In spite of a significant tetravalent antibody response in the MenACWY (± aluminium adjuvant) vaccinated maternal rabbits, and the transfer of strong anti-meningococcal antibody titres to fetuses from the vaccinated rabbits, both adult female rabbits and fetuses exhibited no apparent vaccine-related reproductive or developmental toxicity. Pregnancy in vaccinated maternal rabbits was normal, with no fetal deaths recorded and litters of appropriate number and sex ratio. Fetal body weight was not impacted upon by the high titre of maternal antibody, nor were gross abnormalities observed.

In general, the MenACWY vaccine (Menveo), with and without aluminium adjuvant, posed no detectable reproductive or fetal developmental problems.

Nonclinical Summary and Conclusions

1. Novartis Vaccines and Diagnostics Pty Ltd has applied to register the tetravalent meningococcal vaccine, Menveo, for use in adolescents (≥ 11 years) and adults. The final vaccine preparation contains four meningococcal capsular oligosaccharide antigens, all individually conjugated to the non-toxic *Corynebacterium diphtheriae* protein, CRM_{197}. The meningococcal antigens contained in Menveo are from *N. meningitidis* serogroups A, C, W-135 and Y. From this point onwards, this CRM_{197}-conjugated vaccine will be referred to as MenACWY (and individual antigens referred to as MenA, MenC, MenW & MenY). The final preparation (0.5mL) contains MenA at 10 mg (plus CRM_{197} protein at 12.5 to 33.0 mg), MenC at 5 mg with 6.25 to 12.5 mg CRM_{197}, and MenW and MenY at 5mg with CRM_{197} at 3.3 to 10 mg.

2. Immunogenicity studies in mice showed both strong serum antibody titres and serum bactericidal activity against MenA, C, W-135 and Y CRM_{197} conjugate antigens, particularly after the MenACWY vaccine was delivered with an Al^{3+} containing adjuvant. Similar immunogenicity results were found for intramuscularly vaccinated rabbits, with specific anti-Men antibodies detectable 2-weeks after the final dose. Peak antibody titres were generally detected at Day 42 of the study, after the third vaccine dose. Antibody against the four Men antigens was weakly detectable at Day 14 of the study.

3. Toxicity studies were conducted in rabbits and generally showed no consistent differences between adjuvant alone control rabbits and vaccinated rabbits in terms of clinical pathology markers, histology, organ weights and in-life parameters such as body weights and food consumption. No mortality was recorded for MenACWY-vaccinated rabbits. Only significant reductions in absolute eosinophil and basophil numbers were noted as a consistent difference for rabbits treated with the adjuvanted vaccine versus controls, but in the absence of corresponding differences in neutrophil and total white blood cell numbers, are not likely to be of toxicological significance. It must be noted, however, that rare cases of eosinophilic myocarditis have been associated with meningococcal C vaccines in humans.

4. Reproductive and fetal toxicity studies were performed in rabbits vaccinated with MenACWY (or adjuvant control). No vaccine-associated toxicity was detected in either the maternal rabbits or foetuses. Fetuses had significant anti-MenACWY antibody and SBA titres by the completion of the study, showing the successful transfer of immunity from the mother to the fetuses. In spite of presence of anti-Men responses in the fetuses, no toxicological effects were observed in the fetuses (or mothers). Litter numbers were generally the same

across all vaccine and control groups, no dead fetuses were found and the fetuses were developmentally sound.

5. No carcinogenicity or genotoxicity studies were submitted.

6. In light of the results contained within this report, there are no nonclinical concerns on the capacity for Menveo to induce a tetravalent immune response, and there are no general concerns on vaccine toxicity in animals, including during pregnancy and fetal development. In terms of protective immune response, it must be noted that due to the lack of an appropriate animal model, physiological protection from meningococcal infection after Menveo vaccination can only be extrapolated from SBA data, and thus needs to be considered in this context. The data presented herein, and analysis of the literature, suggest that awareness is also required on the activation of eosinophils post-vaccination (for example eosinophilic myocarditis), as a possible but rare complication in humans receiving meningococcal vaccines.

7. No nonclinical protective efficacy studies were submitted, as there are no suitable animal models of *N. meningitidis* infection, and the demonstration of protective efficacy will depend on clinical data. After due assessment and evaluation of the data, there are no nonclinical concerns on the capacity for Menveo to induce a tetravalent (MenA, C, W-135 and Y) immune response, and there are no general concerns on vaccine toxicity in animals. There are also no general toxicity concerns for Menveo in relation to pregnancy and fetal development.

The data presented herein, and analysis of the literature, also suggest that awareness is also required on the activation of eosinophils post-vaccination, as eosinophil-mediated hypersensitivity complications in humans receiving meningococcal vaccines have been observed and reported in the biomedical literature.

IV. Clinical Findings

Introduction

Menveo is a meningococcal ACWY conjugate vaccine proposed for registration in Australia. The submission was supported by information from 20 clinical studies, consisting of 3 studies assessing clinical pharmacology, 4 pivotal immunogenicity studies, 11 supporting immunogenicity studies, and 2 additional (ongoing) safety studies.

The clinical development plan was clearly identified and described. This plan encompassed a range of age groups from toddlers to adults. As such, only a small number of studies (5) actually involved the proposed target population, adolescents (11 to 18 years) and adults (19 to 55 years), being administered the trial formulations.

Pharmacokinetics

Pharmacokinetic studies were not performed in support of this application. For vaccines, this is not unusual, as pharmacokinetic properties of vaccines do not provide useful information for establishing adequate dosing recommendations.

Drug Interactions

There were no specific Drug Interaction studies submitted with this application.

Pharmacology

Studies assessing clinical pharmacology

V59 P2 (Dose ranging study in toddlers)

This was a phase 2 randomised observer-blind active controlled multicentre dose ranging study to evaluate the immunogenicity and safety of different formulations of conjugate Men ACWY vaccine and conjugate meningococcal C vaccine administered to healthy toddlers aged 12 to 16 months. This study was conducted in Finland and Germany between June 2003 and November 2003. The primary immunogenicity objective of the study was to evaluate the SBA geometric mean titre (GMT) increase at one month after the first study vaccination as compared to baseline values in all subjects.

The secondary immunogenicity objectives were to evaluate the immunogenicity of one and two injections of the different formulations of study vaccines for all serogroups in terms of SBA GMT increase at one month after the second study vaccination compared with baseline values in subjects receiving two doses, percentage of subjects with SBA titre ≥1:4 at one month after the first vaccination in all subjects, percentage of subjects with SBA titre ≥1:4 at one month after the second vaccination in subjects receiving two doses, percentage of subjects with SBA titre ≥1:8 at one month after the first vaccination in all subjects, percentage of subjects with SBA titre ≥ 1:8 at one month after the second vaccination in subjects receiving two doses, percentage of subjects with at least a 4 fold increase of SBA titres at one month after first vaccination compared with baseline values in all subjects, percentage of subjects with at least a 4 fold increase of SBA titres at one month after second vaccination compared with baseline values in subjects receiving two doses, ELISA geometric mean concentration (GMC) before Day one and one month after the first vaccination in all subjects and ELISA GMC before Day one and one month after the second vaccination in subjects receiving two doses.

The safety objective was to evaluate the safety and tolerability of one and two doses of different formulations of all study vaccines. Subjects were healthy toddlers aged 12 to 16 months who were enrolled and randomly assigned in a 1:1:1:1:1:1 ratio to one of the six treatment groups[9]. Within each vaccination group, subjects were also randomised in a 3:1 ratio to receive one or two intramuscular doses of either Men ACWY conjugate vaccine containing different formulations of meningococcal antigens (10 mg, 5 mg, and 2.5 mg) or Men CWY alone (group 2) or Menjugate as control (group 6). Blood was drawn at visit 1 (Day 1 prior to vaccination) and on visit 2 (28 to 35 days after visit 1) in all subjects. Another blood sample was drawn on visit 3 (28 to 35 days after visit 2) in the subset of subjects receiving two doses. Groups 1, 3, 4 and 5 received different formulations of the investigational Novartis Men ACWY vaccine obtained by extemporaneous mixing just before injection of the lyophilized Men A component, re-suspended with the Men CWY full liquid vaccine.

In terms of statistical analysis there was no statistical hypothesis associated with the immunogenicity objectives. All analyses were run descriptively with the aim to suggest a hypothesis to be tested in future properly powered studies. A total of 635 subjects were enrolled in the study and randomised to one of the six study vaccine groups.

With regard to the primary immunogenicity analysis, by 28 to 35 days after the first vaccination, human complement serum bactericidal activity (hSBA) titres in all 4 Men ACWY vaccine groups were highest to serogroup Y, were intermediate to serogroups C and W, and were lowest to serogroup A. Each study vaccine group containing the A antigen was

[9] Five groups given Men ACWY at (in µg) 10-10-10-10, 0-10-10-10 Ad+, 10-5-5-5 Ad+, 5-5-5-5 Ad+, 2.5-2.5-2.5-2.5 Ad+ and one group given Menjugate [Ad+=with adjuvant and Ad-=without adjuvant].

immunogenic (GMT range = 1.89 to 2.83) against serogroup A and the other A antigen containing groups as the 95% confidence intervals for the A10CWY5 group did not overlap those of the other groups. The CWY10 and C10 (Menjugate) control groups did not contain the A antigen, did not raise titres against the A serogroup and were not immunogenic. The immunogenicity results after the first study vaccination showed that the A10CWY5 formulation produced the highest SBA titres against serogroups A and Y among the Novartis Men ACWY formulations during the study.

These results were consistent regardless of the method of measurement used as an indicator of immunogenicity. The Menjugate control produced higher SBA titres against serogroup C than any of the Men ACWY formulations, and the CWY10 formulation without the A antigen produced the highest responses to serogroup W. Approximately 25% of study subjects received a second study vaccination. Results show that the second vaccination boosted the protection afforded by a single vaccination, and higher hSBA titres and higher percentages of subjects achieving 1:4 and 1:8 thresholds against all four serogroups were consistently produced. All Men ACWY formulations were well tolerated and immunogenic in toddlers aged 12 to 17 months.

V59 P4 (Dose ranging study in toddlers and children)

This study was a phase 2 randomised double blind multicentre trial to evaluate the safety and immune response of different formulations of conjugate Men ACWY vaccine with or without aluminium phosphate adjuvant administered to healthy toddlers 12 to 16 months of age and to assess the safety and immunogenicity of a single dose of licensed meningococcal polysaccharide vaccine, Menomune when administered to children 3 to 5 years of age.

This study was conducted in the USA between November 2003 and October 2004. The primary immunogenicity objective was to assess the immunogenicity of a single dose of Men ACWY conjugate vaccine containing 5 mg of each oligosaccharide and formulated with aluminium phosphate adjuvant in comparison with the same formulation without aluminium phosphate adjuvant (percentage of subjects with serum bactericidal activity using human complement of 1:4 or greater against *N. meningitidis* serogroups A, C, W-135 and Y). Secondary immunogenicity objectives were to assess the immunogenicity of a single dose of Men ACWY conjugate vaccine containing 5 mg of each oligosaccharide and formulated with aluminium phosphate adjuvant in comparison with the same formulation without aluminium phosphate adjuvant, to assess the immunogenicity of a single dose of Men ACWY conjugate vaccine containing 5 mg of each oligosaccharide and formulated with aluminium phosphate adjuvant in comparison with the Men ACWY conjugate vaccine containing 10 mg of each oligosaccharide and formulated without the aluminium phosphate adjuvant, to assess the immunogenicity of the Men ACWY conjugate vaccine formulated without aluminium phosphate adjuvant when administered as either 5 or 10 mg of per oligosaccharide, and to assess the immunogenicity of a single dose of licensed Men ACWY polysaccharide vaccine (Menomune) when administered to children 3 to 5 years of age. An additional objective was to evaluate the persistence of antibodies to *N meningitidis* serogroups A,C,W and Y in children approximately 12 months following immunisation with either one dose of Men ACWY conjugate vaccine or one dose of a licensed Meningococcal polysaccharide vaccine.

Subjects in this study were healthy toddlers who were randomised in a 1:1:1 ratio to one of three vaccination groups. Toddler subjects in groups 1 to 3 received a single dose of one of three formulations of Men ACWY conjugate vaccine administered intramuscularly. The protocol was amended to include an additional study group (non-randomised, open label group) of healthy children 3 to 5 years old who received a single dose of licensed Men

ACWY polysaccharide vaccine administered subcutaneously. Statistical methods were limited to a comparison of percentage of responders for the primary immunogenicity objective in Group 2 versus Group 3 against each of the four components. Other comparisons of interest include the percentage of responders in Group 1 versus Group 2, and Group 1 versus Group 3. These comparisons were also made on logarithmically transformed SBA GMTs. A total of 316 subjects were enrolled in the study. The presence of aluminium phosphate adjuvant in Men ACWY 5 mg vaccine did not significantly increase the percentage of responders to any of the four antigens serogroups at Day 29 compared to the non adjuvanted Men ACWY 5mg group. Presence of the adjuvant also did not significantly increase the GMT's to any serogroup although there was a marginally significant trend towards a greater response to serogroup W in adjuvanted than in non adjuvanted 5mg groups.

Non adjuvanted 10 mg and adjuvanted 5 mg Men ACWY groups were virtually identical in the percentage of responders to each of the four serogroups. No trends were apparent that might suggest a difference in response to any serogroup. Non adjuvanted 10 mg and non adjuvanted 5 mg Men ACWY groups were also virtually identical in the percentage of responders and in GMT to serogroups A, C and Y. There was a marginally significant trend towards a greater response to serogroup W in the 10 mg non adjuvanted group than in 5 mg non adjuvanted group in all three measures of immunogenicity. All Men ACWY vaccines were noted to be well tolerated by 12 to 16 month old subjects. Post hoc analysis revealed that immune responses, as measured by percent of responders with hSBA titres ≥1:4 and ≥1:8 and by GMT at Day 29, were higher in each of the Men ACWY groups compared to Menomune, for all four serogroups and most of the differences were statistically significant. The largest differences were observed for serogroups C and Y.

V59 P7 (with and without adjuvant versus Mencevax in toddlers and children)

This study was a phase 2 randomised observer blind multicentre active controlled study to evaluate the safety and immunogenicity of Men ACWY conjugate vaccine (10-5-5-5 µg for A, C, W and Y, respectively, with our without adjuvant) in healthy children aged 12 to 59 months. This study was conducted in Finland and Poland between March 2005 and May 2006.

The primary immunogenicity objective was to compare the functional immune response 28 days after administration of one dose of Men ACWY conjugate vaccine without adjuvant with that of a Men ACWY polysaccharide vaccine as measured by the percentage of subjects with human complement serum bactericidal activity (hSBA) ≥1:4 against *N meningitidis* serogroups A,C,W and Y. The secondary objectives included comparison of the functional immune response 28 days after administration of one dose of Men ACWY without adjuvant with that of the polysaccharide vaccine as measured by geometric mean titres and hSBA≥ 1:8 against *N meningitidis,* persistence of functional immune response 6 or 12 months following administration of one dose of either of the vaccines, and booster effect 21 days after one dose of Men ACWY without adjuvant administered 6 or 12 months after the first dose of either vaccine.

Additional objectives for subjects aged 20 to less than 36 months were to assess the functional immune response 28 days after administration of one dose of either Men ACWY conjugate vaccine with adjuvant or without adjuvant, functional immune response 21 days after the second dose of either Men ACWY with adjuvant or Men ACWY without adjuvant administered one month after the first dose, persistence of functional immune response 6 or 12 months following administration of one dose of either of Men ACWY with or without adjuvant, persistence of functional immune response at 12 months following administration

of two doses of either of Men ACWY with or without adjuvant, and the booster effect 21 days after a second dose of either Men ACWY with or without adjuvant administered 6 or 12 months after the first dose. Subjects were aged between 12 to 60 months and were allocated into one of four vaccination groups according to their specific age; toddlers aged 12 to 35 months were randomised to Men ACWY with adjuvant or without adjuvant and children aged 36 to 59 months were randomised to Men ACWY without adjuvant or Men ACWY polysaccharide vaccine (and received Men ACWY without adjuvant) as the second vaccination. The groups of toddlers were further divided into two sub groups according to their age that is, 12 to 24 months or 25 to 35 months of age. Toddlers aged 12 to 35 months received one dose of Men ACWY with or without adjuvant on Day 1, while children aged 36 to 59 months received one dose of Men ACWY without adjuvant or Men ACWY polysaccharide vaccine on Day 1.

There were no formal statistical hypotheses associated with the immunogenicity objectives and the data were summarised descriptively. At each time point, hSBA GMT's with 95% confidence intervals and the percentage of subjects with hSBA titres≥1:4 and ≥1:8 were calculated. A total of 623 subjects were enrolled in this study. Results of this study for titers ≥1:4 are included as Table 2 below.

The functional immune response, as measured by hSBA, in children aged 36 to 59 months at 28 days after vaccination was higher in subjects who received a Men ACWY without adjuvant compared to those who received the polysaccharide vaccine for all serogroups. Levels of hSBA at 6 and 12 months after vaccination with Men ACWY without adjuvant declined for serogroup A and were moderately low for serogroup C but persisted for serogroups W and Y compared to 28 days after the first vaccination. A second booster vaccination with Men ACWY without adjuvant at 6 or 12 months after the first dose showed very robust responses (greater than 90% achieving an hSBA titre≥ 1:4 for all four serogroups) with GMT's higher in subjects who received the second dose at 12 months. Vaccination with Men ACWY with or without adjuvant to toddlers aged 12 to 35 months resulted in similar immune responses across the four serogroups although the GMT's for serogroups A and C were slightly higher in the group with adjuvant compared to the group without adjuvant. The second vaccination with Men ACWY without adjuvant showed good booster responses (greater than 90% achieving ≥ 1:4) with the highest responses in subjects administered with the second dose 12 months after the first. Persistence of hSBA at 6 or 12 months after the first vaccination was generally low for serogroup A, but higher for serogroup C, W and Y. Following two doses of Men ACWY without adjuvant in toddlers, hSBA persisted in the majority of subjects at 1 year post first dose for groups C, W and Y (hSBA greater than 70%) and declined in serogroup A (29%). Both Men ACWY with and without adjuvant were well tolerated with a lower local reactogenicity profile compared to the polysaccharide vaccine.

Table 2. Primary Immunogenicity Variable: percentage of subjects (95% CI) 36 to 59 months old with hSBA titer ≥1:4 to A, C, W and Y serogroups.

	1st vaccination				**2nd vaccination 6 months after 1st vaccination**		**2nd vaccination 12 months after 1st vaccination**	
	Day 1 (baseline)		Day 29 (28 days after vaccination)		Day 169 (before 2nd)	Day 190 (21 days after 2nd)	Day 337 (before 2nd)	Day 358 (21 days after 2nd)
Sero-group	ACWY ad- N=101	ACWY PS N=81	ACWY ad- N=101	ACWY PS N=81	ACWY ad- N=48	ACWY ad- N=48	ACWY ad- N=45	ACWY ad- N=45
A	2% (0-7)	1% (0.032-7)	75% (66-83)	55% (43-66)	23% (12-37)	92% (80-98)	13% (5-27)	98% (88-100)
C	14% (8-23)	10% (4-19)	60% (49-69)	52% (40-63)	45% (30-60)	100% (92-100)	42% (28-58)	100% (92-100)
W	17% (10-26)	19% (11-29)	91% (84-96)	67% (55-77)	94% (82-99)	100% (92-100)	84% (71-94)	100% (92-100)
Y	10% (5-18)	11% (5-21)	77% (68-85)	67% (56-77)	70% (55-83)	100% (92-100)	80% (65-90)	100% (92-100)

Ad-=without adjuvant. Ad+=with adjuvant. PS=polysaccharide formulation.

Comments on Clinical Pharmacology

· Three phase 2 clinical studies were performed to assess clinical pharmacology in this application, particularly with regard to selection of the final formulation. These studies (V59 P2, V59 P4, and V59 P7) were all randomised, observer or double-blind, controlled studies conducted in toddlers and young children. This obviously differs from the proposed target population of adolescents and adults. These studies were designed to investigate the effect of different doses of each serogroup on the immune response (10 µg to 2 µg), and the need to adjuvant (aluminium phosphate, 0.6mg/mL as Al^{3+}).

· Study V59 P2 was a randomised, observer-blind, controlled study where healthy subjects were randomly allocated to one of six groups. Four groups received one injection of adjuvanted Men ACWY dose of each serogroup ranging from 2.5 µg to 10 µg. One group omitted the serogroup A component and the control group received Menjugate (serogroup C) only. Statistical analysis was limited to descriptive analyses only. Results suggested that the highest responses against serogroup A were those induced by the formulation comprised of 10 µg A antigen with 5 µg from each of the other groups. The immune responses induced by 10 µg of groups C, W and Y were not consistently higher than those induced by 5 µg antigen.

· Study V59 P4 was a randomized, double-blind, controlled study where healthy subjects (toddlers) were randomly allocated to one of four groups. Two groups received Men ACWY 5-5-5-5 µg with or without adjuvant, one group received Men ACWY 10-10-10-10 µg without adjuvant, and the control group (consisting of older children aged 3 to 5 years) received Menomune, a polysaccharide ACWY vaccine. No rationale for the choice of control group was stated in the clinical overview. Statistical analysis was limited to a

comparison between percentages of responders (SBA titres ≥ 1:4) between each of the groups for each of the four components. The percentage of responders was comparable between the adjuvanted and non-adjuvanted formulations for all four serogroups. For percentage of subjects with hSBA ≥ 1:8, response was comparable for serogroups A, C and Y, although for serogroup W, the percentage of responders was statistically higher in the adjuvanted group.

· Study V59 P7 was a randomised, observer-blind, controlled study, where healthy subjects (toddlers) were randomly allocated to one of three groups, Men ACWY 10-5-5-5 µg with or without adjuvant, with a group of older children (36 to 59 months) who received either non-adjuvanted Men ACWY 10-5-5-5, or a polysaccharide meningococcal vaccine (Mencevax). Statistical methods were limited to descriptive analyses only. All subjects received a second dose of Men ACWY with or without adjuvant at 1 month, 6 months or 12 months. There were no significant differences in the percentage of subjects with hSBA titres ≥ 1:4 between either of the Men ACWY formulations, and similarly in the percentage of subjects with hSBA titres ≥ 1:8.

Efficacy

Pivotal studies assessing Immunogenicity

V59 P13 (Lot-to-lot consistency versus Menactra in Adolescents and adults)

This study was a phase 3 randomised observer blind controlled multicentre study to evaluate the lot-to-lot consistency of Men ACWY conjugate vaccine when one dose is administered to healthy adolescents 11 to 18 years of age and to compare the safety and immunogenicity of Men ACWY conjugate vaccine with that of a licensed Men ACWY conjugate vaccine (Menactra) when one dose is administered to healthy subjects 11 to 55 years of age. This study was conducted in the USA between March 2007 and January 2008.

The primary immunogenicity objectives at 1 month after a single injection were to show consistency of immune response for three lots of Men ACWY as measured by SBA GMT response using human complement directed against *N meningitidis* serogroups A,C,W-135 and Y; to compare immunogenicity of a single injection of Men ACWY (three lots combined) to that of a single injection of Menactra defined as the percentage of subjects with seroresponse directed against *N meningitidis* serogroups A,C,W-135 and Y; and to compare the immunogenicity of a single injection of Men ACWY (three lots combined) to that of a single injection of Menactra, defined as the percentage of subjects with seroresponse directed against *N meningitidis* serogroups A,C,W-135 and Y in healthy adults 19 to 55 years of age.

Secondary immunogenicity objectives at one month after a single injection were to assess the consistency of immune response to three lots of Men ACWY as measured by the percentage of subjects with seroresponse, (hSBA ≥ 1:4 and ≥ 1:8) in healthy adolescents 11 to 18 years of age; to compare immunogenicity of a single injection of a Men ACWY (three lots combined) to that of a single injection of Menactra, defined as the percentage of subjects with seroresponse directed against *N meningitidis* serogroups ACW-135 and Y in healthy subjects 11 to 55 years of age; to compare the immunogenicity of a single injection of Men ACWY (three lots combined) to that of a single injection of Menactra, defined as the percentage of subjects with hSBA ≥ 1:4 and ≥ 1:8 in subjects 11 to 55 years of age; and to compare immunogenicity of a single injection of a Men ACWY (three lots combined) to that of a single injection of Menactra as measured by hSBA GMTs in healthy subjects 11 to 55 years of age.

The primary safety objective was to compare the percentages of subjects presenting at least one severe systemic reaction to Men ACWY to the percentages of subjects presenting at least

one severe systemic reaction to Menactra during the first seven days following a single injection administered to healthy subjects 11 to 55 years of age. The secondary safety objective was to describe and compare the safety profile following a single injection of Men ACWY (three lots combined) to that following a single injection of Menactra administered to healthy adolescents or adults 11 to 55 years of age. A total of 3,539 subjects 11 to 55 years of age were randomised at a 1:1:1:1 ratio to one of four vaccine groups (Men ACWY, lot 1, lot 2, lot 3 or Menactra). A total of 2180 adolescents (11 to 18 years of age), 413 adults (19 to 34 years of age) and 946 adults (35 to 55 years of age) were enrolled.

The primary immunogenicity criterion for evaluation was that the immunogenicity of the three lots of Men ACWY was considered equivalent if, for each serogroup and each pair of vaccine lots, the two sided 95% confidence interval of the ratio of the GMTs one month after the vaccination was within the interval 0.50, 2.0. The second primary immunogenicity criteriion for evaluation was that the immunogenicity of Men ACWY (three lots combined) was considered non-inferior to the immunogenicity of Menactra in the 11 to 18 year old and the 19 to 55 year old groups for any of the 4 serogroups if the lower limit of the two sided 95% confidence interval around the difference of the percentage of subjects with seroresponse for that group (Men ACWY minus Menactra) was greater than -10%. A Men ACWY serogroup was considered to have a statistically significant higher immune response compared with that same serogroup of Menactra if the lower limit of the two sided 95% confidence interval around the difference in percentage of seroresponders was greater than 0.

The first of the primary objectives demonstrated consistency among the three Men ACWY lots for all four serogroups (that is, for all 3 pair wise comparisons the two sided 95% confidence interval of the ratio of the GMT's was within the interval 0.5, 2.0). The other two co-primary objectives showed that the seroresponse to the Men ACWY was non inferior to that of Menactra for all four sub groups both in the 11 to 18 and the 19 to 55 age stratification (that is, the lower limit of the two sided 95% confidence interval around the difference in the percentages of seroresponders was greater than -10%). In addition, seroresponse to Men ACWY was demonstrated to be superior (two sided 95% confidence interval was greater than 0%) to that of Menactra for serogroups AW and Y in the 11 to 18 age group and for serogroups CW and Y in the 19 to 55 age group. The primary safety objectives demonstrated that Men ACWY was non inferior to Menactra in terms of severe systemic reactions (the upper limit of the two sided 95% confidence interval of the difference in the percentage of subjects that experienced at least one severe reaction was below 6%). Both study vaccines were well tolerated.

V59 P18 (With and without Boostrix and Gardasil in Adolescents)

This study was a phase 3 single centre open label controlled randomised study to evaluate the safety and immunogenicity of Men ACWY vaccine administered either alone or concomitantly with a combined tetanus, reduced diphtheria toxoid, acellular pertussis vaccine (Boostrix or Tdap) and quadrivalent human papilloma virus (HPV; Type 6, 11, 16, 18) recombinant vaccine (Gardasil) in healthy adolescents. This study was conducted in Costa Rica between July 2007 and February 2008.

The primary immunogenicity objective of the study was to demonstrate that the immune response to Men ACWY as measured by the percentage of hSBA sera responders, when given concomitantly with Boostrix and Gardasil, is not inferior to the immune response when Men ACWY is administered alone; to demonstrate that the immune response to Men ACWY, as measured by the percentage of hSBA seroresponders when given one month after Boostrix, is not inferior to the immune response when Men ACWY is administered alone; to demonstrate that the immune response to Boostrix, as measured by the percentage of subjects

with anti-diphtheria and anti-tetanus toxoid is ≥ 1.0 infectious units (iu) per ml and anti-pertussis toxoid (PT), anti-FHA (Filamentous hemagglutinin) and anti- pertactin (PRN) antigen GMC's when given concomitantly with Men ACWY and Gardasil (HPV) is not inferior to the immune response when Boostrix is administered alone.

The secondary immunogenicity objectives were to demonstrate that the immune response to the HPV vaccine given concomitantly with Men ACWY and Boostrix is not inferior to the immune response to HPV administered alone; to demonstrate that the immune response to Boostrix, as measured by the percentage of subjects with anti-diphtheria and anti-tetanus toxoid were ≥ 1.0 iu infectious units per ml and anti-PT, anti-FHA and anti-PRN GMCs when administered one month after Men ACWY, is not inferior to the immune response to Boostrix administered alone; to assess the immune responses to Men ACWY, as measured by the hSBA GMTs and hSBA titres, are ≥ 1:8 and ≥ 1:4 when given a) concomitantly with Boostrix and Gardasil, and b) when given one month after Boostrix; and to assess the anti-diptheria and anti-tetanus GMCs and percentage of subjects with a four fold rise of antibodies titre over baseline against PT (pertussis toxoid), FHA and PRN.

The safety objectives of the study were to assess the safety profile following a single injection of Men ACWY, given alone one month after Boostrix, compared with the safety profile following a single injection of Men ACWY given alone one month before Boostrix; to assess the safety profile following a single injection of Men ACWY given alone or concomitantly with Boostrix and Gardasil; and to assess the safety profile following a single injection of Gardasil given alone or concomitantly with Boostrix and Men ACWY. Subjects were randomised at a 1:1:1 ratio to receive either:

a) Men ACWY concomitantly with Boostrix and Gardasil at study month 0 followed by two injections of Gardasil at Months 2 and 6,

b) Men ACWY at study month 0 followed by one injection of Boostrix at Month 1, followed by three injections of Gardasil at Months 2, 4, 8, and

c) Boostrix at Month 0, followed by one injection of Men ACWY at Month one, followed by three injections of HPV at Months 2, 4 and 8.

Randomisation was stratified by gender and age group (11 to 14 years of age and 15 to 18 years of age). A total of 1,620 subjects were enrolled and vaccinated. Subjects were healthy male or females aged between 11 and 18 years of age.

Primary criteria for evaluation included concomitant non-inferiority for Men ACWY (lower limit of the two sided 95% confidence interval of the difference in the percentage of seroresponders for each group to be less than -10%), concomitant non-inferiority for Boostrix (lower limit of the two sided 95% confidence interval around the difference of the percentages of subjects with ELISA anti-D toxoid and anti-T toxoid ≥ 1.0 iu infectious units per ml to be greater than -10%; lower limit of the two sided 95% confidence interval for the vaccine group ratios of the anti- PT, anti-FHA and anti-PRN GMCs to be greater than 0.67) and sequential non-inferiority for Men ACWY (lower limit of the two sided 95% confidence interval of the difference in the percentage of seroresponders for each group to be greater than -10%). Results of this study are included as Table 3. These studies are ongoing and therefore interim results were only provided and analysed.

Table 3. Primary immunogenicity objective: Effect of concomitant and sequential* vaccination on immunogenicity of diptheria, tetanus and pertussis antigens (postvaccination results)

% (95% CI)	**MenACWY+Tdap+ HPV (I)**	**MenACWY →Tdap (II)**	**Tdap→ MenACWY [a](III)**	**Vaccine Group difference (I-III)**	**Vaccine Group Ratio (I/III)**	**Vaccine Group Difference (II-III)**	**Vaccine Group Ratio (II/III)**
	N=495	N-459	N=487	**concomitant**		**Sequential**	
Diptheria % ≥1 iu/mL	100 (99, 100)	100 (99, 100)	98 (96, 99)	2 (1, 4)	NA	2 (1,)	NA
Tetanus % ≥1 iu/mL	100 (99, 100)	100 (99, 100)	100 (99, 100)	0 (-1, 1)	NA	0 (-1, 1)	NA
GMC Pertussis antigen							
PT	N=482 51 (47, 55)	N=452 79 (73, 79)	N=477 63 (58, 69)	NA	0.8 (0.71, 0.9)	NA	1.25 (1.11, 1.42)
FHA	N=492 341 (310, 375)	N=458 1107 (989, 1238)	N=485 511 (464, 63)	NA	0.57 (0.58, 0.76)	NA	2.22 (1.91, 2.59)
PRN	N=495 824 (732, 928)	N=459 1563 (1390, 1758)	N=487 1198 (1063, 1351)	NA	0.69 (0.58, 0.81)	NA	1.32 (1.13, 1.55)

[a]Tdap alone. *Secondary objective

The two co-primary Men AWYC immunogenicity objectives demonstrated that Men ACWY can be administered either concomitantly with Boostrix and Gardasil or sequentially one month after Boostrix without a clinical meaningful impact on the immune response relative to Men ACWY administered alone. The co-primary Boostrix immunogenicity objective showed that the immunogenicity of Boostrix administered concomitantly with Men ACWY and HPV is non inferior to that of Boostrix administered alone for diphtheria, tetanus and for the PT pertussis antigen. Non inferiority was not demonstrated for the FHA and PRN pertussis antigens. The safety profile of Men ACWY was comparable when Men ACWY was administered alone or concomitantly with Boostrix and Gardasil, or one month after Boostrix. The safety profile of Boostrix was comparable when Boostrix was administered alone and concomitantly with Men ACWY and Gardasil. Overall, reactogenicity after Boostrix was higher than after Men ACWY.

V59 P6 (One dose versus Menomune in Adolescents)

This study was a phase 2 randomised single blind controlled multicentre study to compare the safety and immune response of one dose of Men ACWY conjugate vaccine with or without aluminium phosphate adjuvant with the safety and immune response of one dose of licensed Men ACWY polysaccharide vaccine (Menomune) administered to healthy adolescents 11 to 17 years of age. This study was conducted in the USA between October 2004 and March 2006.

The primary immunogenicity objective of the study was to compare the immunogenicity of a single dose of either the adjuvanted Men ACWY or un-adjuvanted Men ACWY with the

immunogenicity of a single dose of licensed Men ACWY polysaccharide vaccine (Menomune) defined as the percentage of subjects with serum bactericidal activity directed against *N meningitidis* serogroups A, C, W-135 and Y at one month after vaccination when administered to adolescents 11 to 17 years of age. The secondary objectives were to compare the immunogenicity of a single dose of either the Men ACWY with or without adjuvant with the immunogenicity of a single dose of licensed ACWY polysaccharide vaccine defined as SBA GMT antibody response directed against *N meningitidis* serogroups A,C,W-135 and Y at one month after vaccination when administered to adolescents 11 to 17 years of age; to evaluate the immunogenicity of a single dose of either the Men ACWY with or without adjuvant and the immunogenicity of a single dose of Menomune defined as the percentage of subjects with hSBA≥ 1:4; to evaluate the immunogenicity of a single dose of either the Men ACWY with or without adjuvant and the immunogenicity of a single dose of Menomune defined as SBA GMT antibody response directed against *N meningitidis* serogroups A,C,W-135 and Y at twelve months after vaccination; and exploratory analyses of the quality and quantity of memory B cells in the peripheral blood in a subset of subjects at 12 months after vaccination using a meningococcal capsule specific B Cell ELISPOT assay[10]. According to the original protocol, healthy adolescents were to be enrolled and randomised to Men ACWY with adjuvant or Menomune vaccination groups. Due to the addition of a third study group after enrolment began, the study was divided into two stages, the first stage randomised subjects to Men ACWY with adjuvant or Menomune in a 1:1 ratio, the second stage randomised subjects to Men ACWY without adjuvant or Menomune in a 4:1 ratio. A total of 524 subjects were enrolled with 334 in stage 1 and 190 in stage 2.

Criteria for evaluation for immunogenicity were the ability of Men ACWY conjugate vaccine to elicit functional SBA against each serogroup in the presence of human complement. For each serogroup hSBA was expressed as the GMT and the percentage of subjects with hSBA response ≥ 1:4. Additional analyses were performed to further describe the bactericidal response. Measures of safety used in this study consisted of local and systemic reactions and other adverse events. The null hypothesis associated with the primary immunogenicity objective was that the proportion of subjects who were responders (hSBA titre ≥ 1:4) to Men ACWY (either adjuvanted or unadjuvanted) at one month after vaccination was inferior to the proportion of subjects who were responders to Menomune for the same group. A given Men ACWY serogroup was determined to be non inferior to that serogroup of Menomune if the lower limit of the two sided 95% confidence interval around the difference in proportions was greater than -10%. This was equivalent to a one sided 97.5% confidence interval.

Men ACWY with and without adjuvant vaccine groups was found to be non inferior to Menomune in the percentage of subjects with hSBA titres≥ 1:4 for all serogroups. Both Men ACWY groups had significantly higher percentages of subjects with hSBA titres≥ 1:4 than Menomune against serogroups A, C and Y at one month after vaccination. Similar results were observed for all 4 serogroups when a more stringent cut off of hSBA≥ 1:8 was used in the assay as both Men ACWY groups were non inferior to Menomune at one month after vaccination. The Men ACWY without adjuvant vaccine group exhibited a significantly greater percentage of subjects with hSBA titres≥ 1:4 at 12 months after study vaccination

[10] ELISPOT is an immunological assay based on ELISA (*Enzyme-Linked Immunosorbent Assay*). Basically, the difference between the two is that in ELISA, the substance containing the "unknown" is stuck at the bottom of the well, whereas in ELISPOT the substance with the "unknown" is placed in the well after the bottom of the well has been coated with cytokine-specific antibody. In both cases, the wells are typically contained within a generic microtiter plate. The ELISPOT method is most often used to determine the amount (that is, the concentration) of activated antigen-specific cytotoxic T-cells in a given sample of splenocytes harvested from immunized animals, usually mice.

than the Menomune group against serogroups C and Y and was comparable with Menomune for serogroup A. The Men ACWY without adjuvant vaccine group had significantly higher SBA GMTs than the Menomune group against the serogroups W and Y at 12 months after vaccination. (Table 4) Against serogroups A and C, GMTs were not significantly different between Men ACWY without adjuvant and Menomune groups (Table 4). A single dose of Men ACWY with or without adjuvant was well tolerated by healthy adolescents. No serious adverse events were related to study vaccine administration.

Table 4. hSBA GMTs at 1 month and 12 months after vaccination [Study V59 P6].

Serogroup	GMT, 95% CI, N	MenACWY-	Menomune	P values
A	1 month GMT 95% CI, N	33 25-44, 140	7.31 5.64-9.47, 149	<0.001***
	12 month GMT 95% CI, N	4.24 3.35-5.38, 140	5.65 4.54-7.03, 149	0.086
C	1 month GMT 95% CI, N	59 39-89, 140	28 19-41, 147	0.005**
	12 month GMT 95% CI, N	28 19-41, 140	26 18-37, 147	0.77
W	1 month GMT 95% CI, N	48 37-62, 138	28 23-36, 141	0.001**
	12 month GMT 95% CI, N	40 31-52, 138	17 13-22, 141	<0.001***
Y	1 month GMT 95% CI, N	92 68-124, 139	35 27-47, 147	<0.001***
	12 month GMT 95% CI, N	30 22-41, 139	13 9.49-17, 147	<0.001***

CI=confidence interval. N=number of subjects per group who have results before, at 1 month, and at 12 months after vaccination. *=p<0.05, **P<0.01, ***P<0.001

V59 P11 (With and without Boostrix and Gardasil in Adults)

This study was a phase 3 multicentre observer blind controlled randomised study to compare the immunogenicity and safety of the concomitant administration of a combined tetanus reduced diphtheria and acellular pertussis vaccine (Boostrix) and Men ACWY conjugate vaccine with either one dose of Boostrix or one dose of Men ACWY conjugate vaccine in healthy subjects aged 11 to 25 years. This study was conducted in Italy between April 2006 and May 2007.

The primary objective was to demonstrate noninferiority of Boostrix (Tdap) given concomitantly with MenACWY compared to Tdap administered concomitantly with saline placebo. Secondary objective was to evaluate immune response of MenACWY administered concomitantly with Tdap versus concomitant administration of MenACWY and saline placebo. The immune response of MenACWY was explored as a descriptive analysis in a subset of randomly selected subjects (only data for subjects aged 11 to 18 years are included here),.

Safety objectives were to compare the safety profile following a single injection of Men ACWY administered with Boostrix to that of either Boostrix administered with saline placebo or Men ACWY administered with a saline placebo in healthy subjects 11 to 25 years of age. Subjects were randomised at a 1:1:1 ratio to receive concomitant administration of either Boostrix and Men ACWY vaccines or Boostrix vaccine with saline placebo or Men ACWY with saline placebo. A total of 1,072 subjects were enrolled and randomised to receive Boostrix and Men ACWY, Boostrix and saline placebo, and Men ACWY and saline placebo.

The primary immunogenicity criteria of evaluation were percentage of subjects one month after injection with antibody levels against a diphtheria toxoid ≥ 1.0 iu infectious units per ml, tetanus toxoid ≥ 1.0 iu infectious units per ml, seroresponse (four fold increase) against pertussis toxoid, FHA and PRN. Secondary criteria of evaluation were percentage of subjects with antibody levels as determined by ELISA against diphtheria and tetanus toxoid≥ 1.0 iu per ml at one month post vaccination, anti-diphtheria, anti-tetanus, anti-PT, anti- FHA and anti-PRN geometric mean antibody concentration at baseline and at one month after vaccination and GMC increase from baseline at one month after vaccination; and percentages of subjects with hSBA seroresponse against *N meningitidis* serogroup A,C,W and Y at one month after vaccination, percentages of subjects with hSBA titres≥ 1.4 and hSBA titres ≥ 1.8 against *N meningitidis* serogroup ACW and Y at one month after vaccination; hSBA GMT against *N meningitidis* serogroups A,C,W and Y at baseline and one month after vaccination and hSBA GMR (Geometric Mean Ratio) from baseline and at one month after vaccination.

Safety evaluation consisted of percentages of subjects with reported solicited and unsolicited adverse events. The immunogenicity of Boostrix when given concomitantly with Men ACWY was considered non inferior to that of Boostrix when administered with saline placebo if for all 5 antigens the lower limit of the two sided 95% confidence interval for the difference in the response percentage was greater than -10%. The null hypothesis associated with primary immunogenicity objective was that for at least one antigen common to the underlying percentage response in the group receiving Boostrix and Men ACWY was at least 10% lower than the one in the group receiving Boostrix and saline placebo.

The primary objective was achieved with diphtheria, tetanus and FHA but was not met for PT or PRN since the lower limit of the two sided 95% confidence interval of the difference in the percentage of responders was below -10%. A robust immune response was observed for Boostrix antigens (including PT and PRN) regardless of whether a concomitant vaccine was administered.

In subjects tested for Men ACWY immunogenicity, increases in GMTs as determined by hSBA induced by Men ACWY when administered concomitantly with either Boostrix or saline placebo were evaluated. Similar responses to Men ACWY were observed for serogroups C,W and Y regardless of a concomitant vaccine or placebo administration. GMTs against serogroup A increased sixteen fold after Men ACWY was administered concomitantly with Boostrix and twenty-three fold when administered concomitantly with saline placebo. The percentages of subjects with hSBA titres≥ 1.4 and ≥ 1.8 were similar. Compared directly to Boostrix, Men ACWY was well tolerated with a lower reactogenicity profile.

Other studies assessing Immunogenicity

V59 P1 (Two Men ACWY formulations versus Mencevax in Adults)

This was a phase 1 open label randomised single centre active controlled study to evaluate the safety and immunogenicity of one dose of either meningococcal conjugate ACWY vaccine or separate but concomitant administration of the lyophilised meningococcal A component reconstituted with aluminium phosphate as adjuvant and meningococcal CWY liquid vaccine or polysaccharide Men ACWY vaccine in healthy adult subjects. This study was conducted in Switzerland between November 2002 and December 2002.

The primary objective of the study was to evaluate the safety of a single dose of Men ACWY, meningococcal A plus CWY and Mencevax vaccines. Secondary objectives were to evaluate immunogenicity by calculating serum bactericidal activity GMT increases after 28 to 35 days, the percentages of subjects with SBA titres≥ 1:4 before Day 1 and 28 to 35 days after vaccination, and the percentages of subjects with SBA titres≥ 1.8 before Day 1 and after 28 to 35 days. Subjects were enrolled and randomised in a 1:1:1 ratio to receive one dose of either Men ACWY or Men A plus CWY or Mencevax vaccine. Subjects were healthy adults aged between 18 and 45 years of age. A total of 90 subjects were enrolled, 30 in each group. Statistical methods in this study were limited to descriptive analysis only.

At Day 29 the percentage of subjects with human complement SBA titres≥ 1:4 for each serogroup ranged between 90% and 100% in the investigational vaccination groups and between 83% and 100% in the control group. The percentage of subjects from each vaccination group with SBA titres≥ 1:8 for each serogroup ranged between 93% and 100%. Vaccines were noted to be safe and well tolerated in the 90 healthy adults in this study. There were no significant differences between the three groups.

V59 P1E1 (Persistence of antibodies with Mencevax)

This study was an extension of the previously described V59 P1 and was a phase 2 open label single centre controlled study to evaluate the anamnestic response of healthy adults previous vaccinated with either meningococcal ACWY conjugate vaccine or Mencevax after challenge with a reduced dose of a polysaccharide meningococcal ACWY vaccine. This study was conducted in Switzerland between November 2003 and December 2003.

The objectives of this study were to evaluate the serum antibody responses to serogroups ACWY 28 days following administration of a reduced dose of Men ACWY polysaccharide vaccine at least one year after vaccination with conjugate Men ACWY vaccine or Mencevax vaccine as control. Other immunogenicity objectives were to evaluate the persistence of serum antibodies at least one year after vaccination and to evaluate serum antibody responses to serogroups 7 days following administration of a reduced dose of a polysaccharide Men ACWY vaccine at least one year after vaccination. Approximately 30 healthy adult subjects were to be enrolled with 15 healthy adults previously vaccinated with Men ACWY conjugate vaccine to receive a reduced dose of polysaccharide ACWY vaccine and 15 healthy adult subjects previously vaccinated with Mencevax vaccine to receive a reduced dose of a licensed polysaccharide vaccine. Blood was then taken on Day 1, Day 6, Day 8, Day 15 and Day 29 following vaccination.

The memory immune response to a reduced dose of a polysaccharide ACWY vaccine in subjects previously vaccinated with Men ACWY conjugate vaccine or Mencevax for all 4 serogroups was assessed in terms of serum bactericidal assay, geometric mean titre increases at 7 and 28 days after vaccination, the percentages of subjects with SBA titres≥ 1:4 before Day 1, 7 and 28 days after vaccination, ELISA geometric mean concentration before Day 1, 7

and 28 days after vaccination, the proportion of subjects in each study group that exhibited at least a four fold increase in SBA titre from baseline, the proportion of subjects in each study group who exhibited at least a four fold increase in a specific antibody concentration measured by ELISA from baseline and the results of the assessment by ELISPOT assay and polyclonal stimulation of B cells of the kinetics of plasma cell and memory B cell generation and its correlation to specific serum antibody levels. Statistical analysis was limited to descriptive analysis only.

At baseline, antibody titres in subjects primed with Men ACWY and with Mencevax were similar as determined by serum bactericidal assay GMTs and by the percentages of subjects with a titre ≥ 1:4 or 1:8. The immune response in subjects primed with Men ACWY as measured by SBA GMTs increased (1.45 to 2.15 fold above baseline) on Day 8 after challenge against each of the four meningococcal antigens but a challenge with a reduced dose of polysaccharide ACWY did not induce SBA GMT increases in subjects primed with Mencevax. Antibody titres continued to increase in the Men ACWY primed subjects as evidenced by Day 28 titres 2.04 to 2.79 fold above baseline. This study suggested an anamnestic immune response against all four ACWY meningococcal serogroups in healthy adult subjects previously vaccinated with Men ACWY but not for subjects who received Mencevax in V59 P1. No significant safety trends were noted and there were no serious adverse events.

V59 P3 (With and without adjuvant versus Mencevax in Adults)

This was a phase 1 observer blind randomised single centre controlled study to evaluate the safety and immunogenicity of one dose of Men ACWY conjugate vaccine with aluminium phosphate adjuvant or Men ACWY conjugate vaccine without adjuvant, or polysaccharide Men ACWY vaccine in healthy adult subjects. This study was conducted in Switzerland between July 2003 and August 2003.

The safety objective was to evaluate the safety and tolerability of a single dose of all three vaccines, and the immunogenicity objective was to evaluate the serum antibody response 28 days after administration of a single dose of each vaccine. Subjects were healthy adults aged between 18 and 45 years and were randomly assigned in a 1:1:1 ratio into the three vaccination groups. The immunogenicity criteria for evaluation was in terms of SBA GMT increase at one month after vaccination when compared with baseline values, percentage of subjects with SBA titres ≥ 1:4 before Day 1 and one month after vaccination, percentage of subjects SBA titres ≥ 1:8 before Day 1 and one month after vaccination and ELISA geometric mean concentration before Day 1 and one month after vaccination.

Statistical methods included descriptive statistics as well as ELISA GMC. Median, minimum and maximum concentration for pre vaccination and post vaccination and associated 95% confidence intervals were calculated. A total of 90 subjects were enrolled with 30 in each vaccination group. Evaluation of the immunogenicity criteria was by ELISA only. At baseline the GMCs were similar among the vaccination groups when compared by serogroup. All GMCs increased after vaccination with a GMR for the respective serogroups being (ranges) 5.35-12, 31-44, 34-46, and 47-66. There were no clinically significant safety concerns.

V59 P5 (Schedule finding after one or two doses in infants)

This study was a phase 2 randomised open label controlled multicentre study to evaluate the safety, immunogenicity and induction of immunological memory after two or three doses of Men ACWY conjugate vaccine administered to healthy infants at 2, 3, 4 or 2, 4 and 6 months

of age. This study was conducted in the United Kingdom and Canada between September 2004 and October 2006. The primary immunogenicity objective was to assess the immunogenicity of three doses of Men ACWY conjugate vaccine with adjuvant given at 2, 3 and 4 or 2, 4 and 6 months of age as measured by the percentage of subjects with hSBA≥ 1:4 against serogroups A, C, W and Y. The secondary objectives were to assess immunogenicity as measured by hSBA GMT and hSBA≥ 1:8; to assess immunogenicity of two doses given at 2 and 4 months of age as measured by hSBA≥ 1:4, hSBA ≥ 1:8 and hSBA GMT; to assess immunogenicity of a booster dose of Men ACWY with adjuvant or without adjuvant conjugate vaccine given at 12 months of age in a subgroup of subjects; to assess the persistence of antibodies at 12 months of age in subjects who had previously received two doses of Men ACWY with adjuvant or without adjuvant or Menjugate vaccine; to assess the persistence of antibodies at 12 months of age in subjects who had previously received three doses of Men ACWY conjugate vaccine with adjuvant; to assess the induction of immunological memory by challenge with a reduced dose of polysaccharide Men ACWY vaccine given at 12 months of age; to assess the induction of immunological memory by challenge with a reduced dose of polysaccharide vaccine given at 12 months of age in a subgroup of subjects who previously received two doses of Men ACWY conjugate vaccine with or without adjuvant; to assess the immunogenicity of Men ACWY conjugate vaccine with adjuvant after a three dose regime in comparison to the immunogenicity of Men ACWY conjugate vaccine with adjuvant after a two dose regime; to assess the memory response of Men ACWY adjuvant conjugate vaccine after a three dose regime in comparison to the memory response after a two dose regime; to assess the immunogenicity of routine vaccines when given concomitantly to Men ACWY with adjuvant or without adjuvant conjugate vaccine with the evaluation of titres against HIB, diphtheria, tetanus, pertussis, followed by pneumococcus, polio, hepatitis B and MMR; and to measure the immunogenicity of Men ACWY conjugate vaccine with adjuvant or without adjuvant and that of Menjugate when administered in a two dose regime.

This study was conducted in two phases. In the first phase, 405 subjects were randomised in a 2:2:1:2:2 ratio to one of five vaccination groups to receive either two or three doses of Men ACWY conjugate vaccine with adjuvant or two doses of Menjugate[11]. At 12 to 14 months, subjects belonging to groups 1, 2 and 3 received a booster dose of Men ACWY conjugate vaccine with adjuvant. Subjects belonging to group 5 were randomised in a 1:1 ratio to receive either one booster dose of Men ACWY conjugate vaccine with adjuvant or a challenge dose of a polysaccharide vaccine. Approximately 50% of subjects belonging to group 4 received a reduced dose of meningococcal polysaccharide vaccine. In phase 2, 90 subjects in each country were assigned to a vaccination group. Subjects in group 6 in the UK received two doses of Men ACWY conjugate vaccine without adjuvant concomitantly administered with Boostrix, and subjects in group 7 in Canada received two doses at 2 and 4 months of Men ACWY conjugate vaccine without adjuvant concomitantly with diphtheria, tetanus, acellular pertussis, inactivated polio virus, hepatitis B virus vaccine and Prevnar vaccines. At 12 to 14 months of age, subjects belonging to group 6 received a booster dose of Men ACWY conjugate vaccine without adjuvant and subjects belonging to group 7 were randomised in a 1:1 ratio to receive either one booster dose of Men ACWY conjugate vaccine

[11]Phase 1: Novartis MenACWY Ad+ (with adjuvant) conjugate vaccine was injected in group I (at 2, 4, and 6, and at 12 months), group II (at 2, 4, and 12 months), group III (at 12 months), group IV (at 2, 4, and 6 months), and group V (at 2 and 4 months for all, and at 12 months in a subgroup). Phase 2: Novartis MenACWY Ad- (without adjuvant) conjugate vaccine was injected in group VI (2, 4, and 12 months), and group VII (at 2 and 4 months for all subjects, and at 12 months in a subgroup of subjects). The vaccines used in the United Kingdom and Canada were from identically manufactured lots.

without adjuvant or a reduced dose of meningococcal polysaccharide vaccine. Subjects were healthy 2 month old infants aged between 55 and 89 days at the time of commencement of the study. The criteria for evaluation for immunogenicity were that the functional bactericidal antibody titres against each serogroup were measured using human serum bactericidal assay in the presence of human complement and expressed as hSBA geometric mean titres and percentage of subjects having hSBA≥ 1:4 and ≥ 1:8. Immunogenicity variables for assessing the immune response of concomitant vaccines were also utilised.

The primary immunogenicity objective was to compare the percentage of responders defined as percentage of subjects with hSBA titres≥ 1:4 against each of the serogroups. The null hypothesis associated with the primary immunogenicity objective was that for at least one serogroup the lower limit of the two sided 95% confidence interval of the percentage of subjects with hSBA titre≥ 1:4 at one month after the third dose was less than 70%.

A total of 601 healthy subjects were enrolled. The null hypothesis for the primary objective of the study was rejected based on the findings of the lower limit of the two sided 95% confidence interval of the percentage of subjects with hSBA tiers≥ 1:4 exceeded the criterion 70% for Men ACWY three dose with adjuvant regimes against at least one serogroup (the criterion 70% was met by both groups given three doses vaccine against all serogroups).

The findings supported the conclusion that both the three dose Men ACWY with adjuvant regimes were highly immunogenic against all four serogroups. There was no significant difference between the immunogenic response in Men ACWY with adjuvant or without adjuvant vaccines. A booster dose of Men ACWY conjugate vaccine increased the percentage of subjects with hSBA titres ≥ 1:4 and ≥ 1:8 in the two dose and three dose Men ACWY conjugate vaccine groups. Antibody levels were high against all four serogroups at one month after the booster dose. The persistence of the immune response at 12 months in both two dose Men ACWY vaccine groups was lower against the A serogroup than against the C, W and Y serogroups (8%, 41%, 58%, and 51% against A,C,W and Y serogroups). Routine concomitant vaccines were shown to elicit expected immune responses when given concomitantly with Men ACWY conjugate vaccines in both the UK and Canada. The formulations and schedules of Men ACWY conjugate vaccine were noted to be safe and well tolerated and there were no significant differences between any groups in terms of the incidence or severity of any adverse event.

V59 P8 (versus Menomune in children and toddlers)

This study was a phase 2 randomised single blind controlled single centre study to compare the safety and immunogenicity of one dose of Men ACWY conjugate vaccine with one dose of Men ACWY polysaccharide vaccine (Menomune) administered to healthy children 2 to 10 years of age and an open label study to test the safety and immunogenicity of one dose of Men ACWY conjugate vaccine administered to healthy toddlers 12 to 23 months of age. This study was conducted in the USA between April 2005 and November 2006.

The objective of this study was to compare the immunogenicity of a single dose of Men ACWY conjugate vaccine with the immunogenicity of a single dose of licensed meningococcal polysaccharide vaccine defined as the percentage of subjects with serum bactericidal activity≥ 1:4 directed against serogroups A, C, W -135 and Y at one month after vaccination when administered to healthy children 2 to 10 years of age. The secondary objective was to compare the immunogenicity of a single dose of Men ACWY conjugate vaccine with the immunogenicity of a single dose of licensed meningococcal AWCY polysaccharide vaccine, defined as hSBA Geometric Mean Titre antibody response one month after vaccination when administered to healthy children 2 to 10 years of age; to

compare the immunogenicity of a single dose of Men ACWY conjugate vaccine with a single dose of polysaccharide vaccine, defined as percentage of subjects with serum bactericidal activity ≥ 1:4 one month after vaccination when administered to the following groups of healthy children-2 to 5 years of age and 6 to 10 years of age; to compare the immunogenicity of a single dose of conjugate vaccine with polysaccharide vaccine defined as percentage of subjects with serum bactericidal activity≥ 1:4 at one month and at 1 2 months after vaccination when administered to healthy toddlers 12 to 23 months of age and to healthy children 3 to 5 years of age; to compare the immunogenicity 12 months after vaccination a single dose of conjugate vaccine with polysaccharide vaccine in children, when administered to healthy children 2 to10 years of age overall and within the following age groups, 2 to 5 years of age and 6 to 10 years of age.

This study was conducted in two parts with the first part being a randomised single blind controlled study to evaluate the safety and immune response at one and 12 months following vaccination of one dose of either conjugate or polysaccharide vaccine in healthy children 2 to 10 years of age and the second part was open label with and without concomitant PNC (Pneumococcal protein conjugate vaccine) for toddlers 12 to 15 months of age or with and without concomitant Diptheria, Tetanus, and acellular Pertussis vaccine (DTdaP) for toddlers 16 to 23 months of age. In part 1, healthy children 2 to 10 years of age were randomly assigned to one of two groups in a 1:1 ratio to either receive conjugate or polysaccharide vaccine. In part 2 healthy toddlers 12 to 23 months of age were randomly assigned to one of two groups to receive either conjugate vaccine alone or with concomitant PNC for toddlers 12 to 15 months of age and alone or with concomitant Boostrix for toddlers 16 to 23 months of age in a 1:1 ratio. Subjects were healthy children either aged between 2 and 10 years of age or healthy toddlers 12 to 23 months of age.

The primary immunogenicity objective was to compare the percentage of responders (hSBA ≥ 1:4) in children aged 2 to 10 years at one month after immunisation with conjugate versus polysaccharide vaccine for each of the four serogroup components. The percentage of responders for each of the 4 serogroup components in toddlers aged 12 to 23 months was compared after immunisation with conjugate vaccine alone or in combination with PNC or DTaP for toddlers aged 12 to 15 and 16 to 23 months respectively. A total of 619 children aged 2 to 10 years were enrolled in part 1 of the study and 291 toddlers aged between 12 and 23 months were enrolled and randomised in part 2 of the study.

In children aged 2 to 10 years, as assessed by either the percentage of subjects with hSBA≥ 1:4 or GMTs at one month after vaccination, the conjugate vaccine showed statistically significant superior immune responses compared to the polysaccharide vaccine. At twelve months after vaccination the percentage of subjects was still statistically significant higher after conjugate compared with polysaccharide vaccine. For toddlers aged 12 to 23 months as assessed by either the percentage of subjects with hSBA≥ 1:4 or GMTs at one month after vaccination, the conjugate vaccine showed statistically significant superior immune responses compared to the polysaccharide vaccine. Analysis of toddlers who received conjugate vaccine alone or in combination with PNC or DTdaP showed no substantial differences between the groups with regard to responder rate and GMT. The conjugate vaccine was noted to be well tolerated by 2 to 10 year old children with an adverse event profile consistent with subjects in these age groups. The incidence of local reactions especially erythema and in duration were noted to be higher in the conjugate groups than in the polysaccharide groups whereas there were no differences in systemic reactions between the two groups. Severe reactions were rare in either group.

V59 P9 (Schedule finding after one or two doses in infants)

This was a phase 2 partially randomised open label multicentre study to evaluate the safety and immunogenicity after one or two doses of Men ACWY conjugate vaccine administered to healthy infants and young children. This study was conducted in Canada between June 2005 and November 2006.

The primary immunogenicity objective of the study was to assess the immunogenicity of conjugate vaccine when administered as a two dose schedule at 6 and 12 months of age where immunogenicity was defined as a serum bactericidal assay titre of 1:4 or greater against serogroups A, C, W and Y at one month after the second vaccination. The secondary immunogenicity objectives were to assess the immunogenicity of conjugate vaccine when administered as a one dose schedule at 12 months of age; to assess the immunogenicity of DTaP-HIB-IPV (IPV=Inactivated Polio Vaccine) and PC7 (7-valent pneumococcal CRM-197 conjugate vaccine) routine vaccinations when administered alone or concomitantly with conjugate vaccine at 6 months of age; to evaluate the immune response of meningococcal C conjugate vaccine administered at 12 months of age; to evaluate the primary immunogenicity of the AWY component of Men ACWY vaccine when administered at 18 months of age following one dose of meningococcal C conjugate vaccine previously administered at 12 months of age; to evaluate the booster response of the C component of Men ACWY vaccine when administered at 18 months of age following one dose of meningococcal C conjugate vaccine previously administered at 12 months of age.

Subjects were randomised in a 1:1 ratio to one of two vaccination groups, group 1 receiving conjugate vaccine at 6 and 12 months and group 2 receiving conjugate vaccine at 12 months. Subjects in group 1 received one dose of conjugate vaccine at 6 months of age and one dose at 12 months of age. The conjugate vaccine was given concomitantly with routine infant immunisations (Pentacel) and meningococcal conjugate vaccine at 6 months of age and with PC7 at 12 months of age. Subjects in group 2 did not receive the conjugate vaccine at 6 months of age only Pentacel and PC7 but did receive one dose of conjugate vaccine at 12 months of age concomitantly with PC7. Approximately 50 subjects up to 12 months old at the time of enrolment were included in group 3 and received one dose of meningococcal C conjugate vaccine, Menjugate, concomitantly with PC7. A single dose of Men ACWY conjugate vaccine was then administered to all subjects belonging to group 3 at 18 months of age concomitantly with DTdaP-HIB-IPV. A total of 175 subjects were enrolled and analysed in this study. Subjects enrolled in groups 1 and 2 were healthy infants of 6 months of age. Subjects enrolled in group 3 were healthy subjects of 12 months of age. There was no statistical null hypothesis associated with the primary immunogenicity objective and all immunogenicity analyses were run descriptively.

The conjugate vaccine was noted to be well tolerated and immunogenic using different dosing regimes in infants and young children including administration after prior vaccination with meningococcal C conjugate vaccine. Comparable immunogenicity for serogroup C was demonstrated after a single dose of conjugate vaccine and a single dose of Menjugate at 12 months of age.

V59 P10 (versus Menomune in Children)

This study was a phase 2 randomised observer blind controlled multicentre study to compare the safety of one dose of Men ACWY conjugate vaccine with that of a Men ACWY polysaccharide vaccine (Menomune) in healthy children 2 to 10 years of age. This study was conducted in Argentina between May 2006 and March 2007.

The primary immunogenicity objective of this study was to compare the immunogenicity of a single dose of Men ACWY conjugate vaccine with the immunogenicity of a single injection of polysaccharide vaccine defined as the percentage of subjects with seroresponse in human bactericidal assay when administered to healthy children 2 to 10 years of age.

The primary safety objective was to compare the percentage of subjects presenting at least one severe systemic reaction to the conjugate vaccine with the percentage presenting at least one severe systemic reaction to the polysaccharide vaccine during the first 7 days following a single injection administered to healthy children 2 to 10 years of age. A total of 1,500 healthy children between 2 and 10 years of age were randomly assigned to one of the two vaccine groups at a 2:1 ratio. Subjects were healthy children 2 to 10 years of age. The safety of the conjugate vaccine was considered non inferior to the safety of the polysaccharide vaccine if the upper limit of the two sided 95% confidence interval of the ratio of the proportion of the subjects experienced at least one severe systemic reaction during the first 7 days after vaccination was less than three.

The null hypothesis associated with the safety objective was that the ratio of the proportion of subjects experiencing at least one severe systemic reaction during the first 7 days after vaccination was at least three. With regard to immunogenicity results, these were not provided as serology analysis was still ongoing. With regard to safety results the primary safety objective was not met due to a very small percentage of subjects experiencing severe systemic reactions that is, 1% in the conjugate group and less than 1% in the Menomune group.

V59 P2EI (Men ACWY followed by Mencevax in Toddlers)

This study was an open label active controlled phase 2 single centre study conducted in Finland. The objective of this study was to assess the safety and immune response following one dose of Mencevax 6 months after one dose of Men ACWY conjugate vaccine. This study was an extension of the previously described study V59 P2 and involved 94 subjects who had previously received Men ACWY conjugate vaccine and 25 subjects who had not. Subjects were healthy toddlers aged between 22 and 24 months of age. Results of this study were not provided as part of this dossier.

V59 P2E2 (Men ACWY followed by Mencevax in Toddlers)

This study was an open label active controlled phase 2 single centre study conducted in Finland. The objective of this study was to assess the safety and immune response following one dose of Mencevax 12 months after 1 or 2 doses of Men ACWY conjugate vaccine. Subjects consisted of 175 subjects receiving one dose of Mencevax 12 months after one or two doses of Men ACWY conjugate vaccine and 62 subjects receiving Mencevax only. Subjects were healthy toddlers aged between 24 and 28 months of age. Results of this study were not provided as part of this dossier.

V59 P14 (Men ACWY booster in infants, ongoing)

This study was an open label randomised phase 2 multicentre study conducted in the USA, Argentina and Columbia. The objective of the study was to assess the safety and immune response of meningococcal conjugate vaccine given with US routine infant vaccines followed by meningococcal conjugate vaccine booster versus routine infant vaccines alone followed by two doses of Men ACWY conjugate vaccine in the second year of life. A total of 3,035 subjects received the conjugate vaccine plus routine vaccines whereas 1,521 subjects received the routine vaccines only followed by the Men ACWY conjugate vaccine in the second year

of life. The subjects were healthy infants of two months of age. No results of this study were submitted as part of the dossier.

V59 P16 (Memory B Cell response in infants, ongoing)

This study was an open label randomised phase 2 single centre study conducted in the United Kingdom. The objective of the study was to assess the safety and immune response as well as memory B Cell response to meningococcal conjugate vaccine at 2 and 4 months of age. A total of 216 subjects received the Men ACWY conjugate vaccine. Subjects were healthy infants aged 2 months of age. The study is ongoing and no results were submitted in the dossier.

Comments on Immunogenicity

· In this submission, efficacy of Menveo was inferred from immunogenicity studies evaluating the production of functional bactericidal antibodies against meningococcal serogroups. Seroresponse was defined as:
a) For a subject with pre-vaccination hSBA titre ≥ 1:4 or baseline, and rise in post-vaccination hSBA titre ≥ 1:8, and
b) For a subject with a pre-vaccination hSBA titre ≥ 1:4, and rise in post-vaccination hSBA titre of at least 4 times the pre-vaccination titre.

Other immunological endpoints included hSBA titre ≥ 1:8, hSBA titre ≥ 1:4, hSBA GMT's and Reverse Cumulative Distribution Function (RCDF) curves.

· Four clinical studies were provided to assess immunogenicity. Two of these, V59 P13 and V59 P18, were identified as pivotal. V59 P13 was a non-inferioritynon-inferiority study to assess lot-to-lot consistency between 3 formulations of Menveo, as well as immunogenicity compared with Menactra, a US licensed conjugate Men ACWY vaccine. This vaccine is not registered in Australia. V59 P18 was a non-interference study to assess immunogenicity when Men ACWY is administered concomitantly with other common vaccines given during adolescence, Boostrix (Tdap, tetanus toxoid-diphtheria-acellular pertussis vaccine) and Gardasil (HPV). This study has yet to be completed. Two supporting studies were also identified, V59 P6 (which assessed non-inferiority of Men ACWY against Menomune, a licensed polysaccharide Men ACWY vaccine), and V59 P11 (which was a non-interference study evaluating the immune response of Men ACWY administered concomitantly with Tdap and concomitantly with saline placebo.

· Study V59 P13 was a phase 3, observer-blind, randomised, controlled comparative study designed to demonstrate lot-to-lot consistency between three lots of Men ACWY, and non-inferiority of Men ACWY versus Menactra, a conjugate Men ACWY vaccine licensed in the USA. The three primary objectives were to establish lot-to-lot consistency between 3 lots of Men ACWY with respect to hSBA GMTs in adolescents (11 to 18 years), to demonstrate non-inferiority of Men ACWY compared with Menactra as measured by percentage of subjects with seroresponse in adolescents (11 to 18 years), and to demonstrate non-inferiority of Men ACWY compared to Menactra as measured by percentage of subjects with seroresponse in adults (19 to 55 years). The study was appropriately designed to assess for non-inferiority. Men ACWY was noted to be non inferior to Menactra for all four serogroups, both in adolescents and adults. The primary immunogenicity objective was also met for lot-to-lot consistency.

· Study V59 P18 was an open-label randomised controlled phase 3 study to assess immune response to Men ACWY with and without Boostrix (Tdap) and Gardasil (HPV) vaccines. Subjects were healthy adolescents (11 to 18 years old) who were randomised to receive either Men ACWY concomitantly with Boostrix and Gardasil, Men ACWY with Boostrix on Day 31, or Boostrix at Day 1 followed by Men ACWY on Day 31. The primary objectives were to demonstrate non-inferiority in the percentage of immunoresponders between the first two groups, to demonstrate non-inferiority between the latter two groups in terms of percentage of seroresponders, and to demonstrate non-inferiority of Boostrix when administered concomitantly and alone in terms of seroresponse against specific diphtheria, tetanus and pertussis antigens. This study is ongoing, and no information was available on the interaction with Gardasil. Non inferiority was demonstrated for all the primary objectives.

· Study V59 P6 was a phase 2 randomised, single-blind, comparative study to assess immune response of Men ACWY versus Menomune, a polysaccharide Men ACWY vaccine. Subjects were healthy adolescents (11 to 17 years) who received one injection of either Men ACWY (with or without adjuvant) or Menomune. The study was originally intended to include only Men ACWY (with adjuvant) or Menomune, and a third group (Men ACWY without adjuvant) was added after enrolment began. The study was designed as a non-inferiority study to assess immune response of both Men ACWY groups versus Menomune. Both Men ACWY groups were found to be non inferior to Menomune in the percentage of subjects with hSBA titres $\geq$ 1:4 for all serogroups at one month after vaccination. This was also demonstrated for subjects with hSBA titres $\geq$ 1:8. A comparison was also conducted between Men ACWY without adjuvant and Menomune at 12 months post vaccination, which suggested that Men ACWY without adjuvant had a significantly greater percentage of subjects with hSBA titres $\geq$ 1:4 or at 12 months against serogroups C, W and Y, and comparable to serogroup A, when compared to Menomune.

· Study V59 P11 was a phase 3 non-interference study comparing Men ACWY administered alone and concomitantly with Boostrix (Tdap) in healthy adolescents and adults (aged 11 to 25 years). Subjects were randomised to receive Men ACWY with Boostrix, Men ACWY with saline or Boostrix with saline. The study was designed to assess non-inferiority in terms of immune response to Boostrix, but assessments of immune response to Men ACWY were limited to descriptive analysis (and for a limited number of subjects only). Immune responses to Men ACWY were noted to be comparable whether administered alone or concomitantly for all serogroups. HSBA GMTs induced by Men ACWY given concomitantly with Boostrix were similar for serogroups C, W and Y, and slightly lower for serogroup A, when compared to Men ACWY alone. The primary objective (non-inferiority) was met for response to diphtheria, tetanus and FHA, but not for PT or pertactin.

· Information on 11 other clinical studies was provided. These studies were not identified as supporting the application, as they were either a different formulation, or involved immunisation of a different target population to that proposed. The last two of these studies have not yet been completed (V59 P14 and V59 P16).

· Of particular note are studies V59 P5 and V59 P9, which involved the use of Menjugate, a serogroup C conjugate meningococcal vaccine currently registered in Australia. Study V59 P5 was a phase 2 open-label, randomised controlled study designed to assess scheduling of two or three doses of Men ACWY with concomitant infant routine vaccinations. Subjects were healthy infants of 2 months of age who received one, three or

four injections of Men ACWY. One of the secondary immunogenicity objectives was to compare the immunogenicity of Men ACWY (with or without adjuvant) with that of Menjugate when administered in a two dose regimen, as measured by hSBA≥ 1:4 and hSBA ≥ 1:8 against serogroup C. While this was limited to descriptive analysis only, the immunogenicity (hSBA ≥ 1:4) against serogroup C was significantly higher (98%) at 1 month in the Menjugate group, compared to both Men ACWY groups (with adjuvant 84%, without adjuvant 86%).

· Study V59 P9 was a phase 2 open-label, randomised controlled study designed to assess scheduling of one or two doses of Men ACWY. Subjects were healthy infants between 6 and 12 months old, and were randomised to receive Men ACWY at both 6 and 12 months, or just one dose of Men ACWY at 12 months. Both groups received standard childhood immunisations, and a subset of the second group received Menjugate at 6 months. As such, statistical analysis was limited to descriptive analyses only and results of this study were difficult to interpret. Menjugate with concomitant Prevnar was noted to be highly immunogenic at 12 months of age against serogroup C 1 month later (93% with hSBA≥ 1:4). Subjects receiving two doses of Men ACWY at 6 and 12 months demonstrated percentages of subjects with hSBA titres ≥ 1:4 of 88%, 100%, 100% and 100% against serogroups A, C, W and Y serogroups respectively.

Safety

Pivotal studies assessing safety

V59 P17 (Men ACWY versus Menomune or Menactra in Adults)

This study was a phase 2 randomised observer blind controlled multicentre study to compare the safety and immunogenicity of Men ACWY conjugate vaccine with that of a Men ACWY conjugate vaccine (Menactra) when one dose is administered to healthy subjects 19 to 55 years of age and with that of licensed Men ACWY polysaccharide vaccine (Menomune) when one dose is administered to healthy subjects 56 to 65 years of age. This study was conducted in Argentina and Columbia between May 2007 and February 2008.

The primary objective of the study was to compare the percentage of subjects presenting with at least one severe systemic reaction to Men ACWY conjugate vaccine with the percentage presenting at least one severe systemic reaction to Menactra during the first 7 days following a single dose administered to healthy subjects 19 to 55 years of age. The secondary objectives were to compare the immunogenicity of a single dose of Men ACWY conjugate vaccine with the immunogenicity of a single dose of Menactra at one month after vaccination when administered to healthy subjects 19 to 55 years of age and to compare the immunogenicity of a single dose of Men ACWY conjugate vaccine with the immunogenicity of a single dose of Menomune at one month after vaccination when administered to healthy subjects 56 to 65 years of age.

Additional safety objectives were to describe and compare the percentage of subjects in the Men ACWY conjugate and Menactra vaccine groups and the Men ACWY and the Menomune vaccine groups when administered to healthy adults 19 to 55 years of age and 56 to 65 years of age in terms of immediate hypersensitivity reactions, local and systemic reactions during study Days 1 to 7, adverse events reported during study Days 1 to 29, medically significant adverse events reported during study Days 30 to 180 and serious adverse events reported over the six month follow up period.

Subjects were healthy adults aged between 19 to 55 years and they were randomly assigned to receive either Men ACWY conjugate vaccine or Menactra. Subjects in the 56 to 65 year old

subgroup were randomised in a 2:1 ratio to receive either Men ACWY conjugate vaccine or Menomune. Safety was evaluated in terms of percentage of subjects presenting with at least one severe systemic reaction during the first seven days after vaccination and by describing immediate hypersensitivity reactions following vaccination, local and systemic reactions, body temperature, adverse events and serious adverse events. In terms of statistical analysis, the null hypothesis associated with the safety objective was that the upper limit of two sided 95% confidence interval for the difference in the proportion of subjects experiencing at least one severe systemic reaction during the first 7 days after vaccination between the Men ACWY conjugate and Menactra groups was $\geq 6\%$. The Men ACWY conjugate vaccine was considered non inferior to Menactra with respect to severe systemic reaction if the upper limit of two sided 95% confidence interval for the difference in the proportion of subjects experiencing at least one severe systemic reaction during the first 7 days after vaccination was less than 6%.

A total of 2831 subjects were enrolled and randomised in the study. 2,489 subjects were vaccinated in the 19 to 55 years age group whilst 326 subjects were vaccinated in the 56 to 65 years age group. Results of this study are included as Table 5 below. The primary safety objective to compare the percentage of subjects presenting with at least one severe systemic reaction to Men ACWY conjugate vaccine with the percentage presenting with at least one severe systemic reaction to Menactra during the first 7 days following a single dose administered to healthy subjects 19 to 55 years of age was met. The upper limit of the two-sided 95% confidence interval of the vaccine group difference was 3% which was below the criterion set by the non-inferiority assumption that is, less than 6%. The percentages of subjects reporting solicited adverse events were comparable between the vaccine groups within each age group that is, Men ACWY conjugate versus Menactra in the 19 to 55 years of age and the Men ACWY conjugate vaccine versus Menomune in the 56 to 65 years of age group. The solicited reactions were of short duration with the median duration of all solicited reactions being similar in all vaccine groups.

Table 5. Solicited adverse events (that is, local and systemic reactions collected during the 7 days after vaccination).

Systemic reaction	**Number (%), 95% CI of subjects with solicited reaction**		**MenACWY minus Menactra Vaccine group % difference (95% CI)**	**Primary Safety Objective Criterion** **Upper 95% CI limit <6%**
	19-55 years MenACWY N=1588	**19-55 years Menactra N=882**		
Severe	95 (6%)	46 (5%)	1% (-1, 3)	Met

Age Group	**Type of reaction**	**Number (%) of subjects with solicited reaction**	
		MenACWY N=1588	**Menactra N=882**
19-55 years	Any reaction	955 (60%)	561 (64%)
	Local reaction	729 (46%)	439 (50%)
	Systemic reaction	616 (39%)	375 (43%)
	Other reaction[a]	280 (18%)	162 (18%)
56-65 years		**MenACWY N=1588**	**Menactra N=882**
	Any reaction	124 (57%)	62 (57%)
	Local reaction	92 (43%)	44 (40%)
	Systemic reaction	84 (39%)	44 (40%)
	Other reaction[a]	29 (13%)	15 (14%)

[a]analgesic/antipyretic medications used and stayed at home due to vaccination.

V59 P18 (Men ACWY with and without Boostrix and Gardasil in Adolescents)

This study was a phase 2 single centre open label controlled randomised study to evaluate the safety and the immunogenicity of Men ACWY conjugate vaccine administered either alone or concomitantly with a combined tetanus reduced diphtheria toxoid, acellular pertussis vaccine (Boostrix) and a quadrivalent human papilloma virus (Gardasil) in healthy adolescents. This study was conducted in Costa Rica between July 2007 and February 2008.

The primary immunogenicity objectives were to demonstrate that the immune response to Men ACWY conjugate vaccine as measured by percentage of hSBA seorespondents when given concomitantly with Boostrix and Gardasil is not inferior to the immune response when Men ACWY conjugate vaccine is administered alone; to demonstrate that the immune response to Men ACWY conjugate vaccine when given one month after Boostrix is not inferior to the immune response when Men ACWY conjugate vaccine is administered alone; to demonstrate that the immune response to Boostrix as measured by the percentage of subjects with anti-diphtheria and anti-tetanus toxoids $\geq 1.0\mu$ per ml and anti-PTA, anti-FHA and anti-PRN GMCs when given concomitantly with Men ACWY and Gardasil is not inferior to the immune response when Boostrix is administered alone.

The secondary immunogenicity objectives were to demonstrate that the immune response to Gardasil given concomitantly with Men ACWY conjugate vaccine and Boostrix is not inferior to the immune response when Gardasil is administered alone; to demonstrate that the immune response to Boostrix when administered one month after Men ACWY conjugate vaccine is not inferior to the immune response to Boostrix administered alone; to assess the immune responses to Men ACWY conjugate vaccine when given concomitantly with

Boostrix and Gardasil and when given one month after Boostrix and to assess the anti-diphtheria and anti-tetanus GMCs and the percentage of subjects with a four-fold increase in antibody titre over baseline against PT, FHA and PRN.

The safety objectives were to assess the safety profile following a single injection of Men ACWY conjugate vaccine given alone one month after Boostrix compared with the safety profile following a single injection of Men ACWY conjugate vaccine given alone one month before Boostrix; to assess the safety profile following a single injection of Men ACWY conjugate vaccine given alone or concomitantly with Boostrix and Gardasil and to assess the safety profile following a single injection of Gardasil given alone or concomitantly with Boostrix and Men ACWY conjugate vaccine. Subjects were randomised to a 1:1:1 ratio to receive Men ACWY conjugate vaccine concomitantly with Boostrix and Gardasil at study month zero followed by two injections of HPV at Month 2 and 6; Men ACWY conjugate vaccine at study month zero followed by one injection of Boostrix at Month 1 followed by three injections of Gardasil at Months 2,4 and 8 and finally, Boostrix at Month zero followed by one injection of Men ACWY at Month 1 followed by three injections of Gardasil at Months 2, 4 and 8. Subjects were healthy male or female individuals aged between 11 and 18 years of age.

The primary immunogenicity criteria for evaluation were concomitant non-inferiority for Men ACWY conjugate vaccine – the lower limit of the two sided 95% confidence interval of the difference in the percentages of seroresponders for each serogroup to be greater than -10%, concomitant non-inferiority for Boostrix –the lower limit of the two sided 95% confidence interval around the difference in the percentages of subjects with ELISA anti-D and anti-T toxoids $\geq$ 1.0 µg per ml to be greater than -10%, the lower limit of the two sided 95% confidence interval for the vaccine group ratios of anti-PT, anti-FHA, anti-PRN GMCs to be greater than 0.67 and finally, sequential non-inferiority for Men ACWY conjugate vaccine – the lower limit of the two sided 95% confidence interval of the difference in percentages of seroresponders for each serogroup to be greater than -10%.

The measures of safety used in this study consisted of solicited local and severe systemic reactions and other unsolicited adverse events. The safety objectives were evaluated descriptively. A total of 1,620 subjects were enrolled and randomised at a 1:1:1 ratio to one of the three vaccine groups. With regards to the immunogenicity analyses, non-inferiority of the immune response to Men ACWY conjugate vaccine when administered concomitantly with Boostrix and Gardasil compared with the immune response to Men ACWY when administered alone was demonstrated for all four serogroups.

The null hypothesis associated with the primary concomitant non-inferiority objective for Men ACWY was rejected. Non inferiority of the immune response for Men ACWY when administered one month after Boostrix compared with the immune response for Men ACWY when administered alone was demonstrated for serogroups A,C and Y but not for serogroup W. Although the sequential non-inferiority criterion was not met for serogroup W, among subjects lacking bactericidal antibodies at baseline the percentage of seroresponders in the sequential administration group was high (90%). One month after Men ACWY conjugate vaccine, 95% of the subjects receiving Men ACWY conjugate vaccine one month after Boostrix had hSBA titres $\geq$ 1:8 for serogroup W versus 99% of subjects receiving Men ACWY conjugate vaccine one month before Boostrix.

The null hypothesis associated with the primary sequential non-inferiority objective for Men ACWY conjugate vaccine was not rejected. Non inferiority of the immune response to Boostrix when administered concomitantly with Men ACWY conjugate vaccine and Boostrix compared with the immune response to Boostrix when administered alone was demonstrated

for diphtheria, tetanus and PT pertussis antigens but not for FHA and PRN. The null hypothesis associated with the primary concomitant non-inferiority objective for Boostrix was not rejected. With regards to safety, Boostrix was noted to be generally more reactogenic than Men ACWY (69% of subjects reported reactions to Men ACWY versus 82% to Boostrix both administered alone). The most frequently reported local reaction for all vaccines was pain (45% Men ACWY conjugate vaccine alone to 71% Boostrix alone).

The safety profile of Men ACWY conjugate vaccine was comparable when Men ACWY conjugate vaccine was administered alone concomitantly with Boostrix and Gardasil for one month after Boostrix. Similarly the safety profile of Boostrix was comparable when Boostrix was administered alone and concomitantly with Men ACWY conjugate vaccine and Gardasil.

Information from other clinical studies on safety

Information on safety was collected in all clinical studies. The safety profile of a single injection of the final formulation of Men ACWY conjugate vaccine (non adjuvanted Men ACWY conjugate vaccine containing serogroup A, C, W and Y antigens in doses of 10 mg, 5 mg, 5 mg and 5 mg respectively) was evaluated in 3579 adolescents aged 11 to 18 years and 2606 adults aged 19 to 55 years in three pivotal studies (V59 P13, V59 P17 and V59 P18) in support of the studies V59 P6 (adolescents 11 to 17 years of age) and V59 P11 (adolescents and adults 11 to 25 years of age). In addition to this safety data, serious adverse events were provided for studies in which subjects were outside the 11 to 55 year range and/or administered Men ACWY conjugate vaccine formulation that was studied for dose antigen or adjuvant selection purposes.

In the following studies, single or multiple injections of final or non final formulations were administered in subjects in the following age groups, V59 P1 (adults 18 to 45 years), V59 P2 (toddlers aged 12 to 16 months), V59 P3 (aged 18 to 45 years), V59 P4 (toddlers aged 12 to 15 months), V59 P5 (infants aged two months), V59 P7 (toddlers aged 12 to 35 months and children aged 36 to 59 months), V59 P8 (children aged 2 to 10 years and toddlers aged 12 to 23 months), V59 P9 (infants aged 6 to 12 months), V59 P10 (children aged 2 to 10 years), ongoing study V59 P14 (infants aged 2 months), ongoing study V59 P16 (infants aged 2 months) and ongoing study V59 P18 (adolescents aged 11 to 18 years, follow up after Day 61). With the three ongoing studies, serious adverse events based on the safety database as of February 15th 2008 were listed and evaluated. Overviews of studies providing safety data, reactogenicity and adverse events are included in Tables 6-12 below.

Table 6. Overview of studies providing MenACWY safety data.

Region	**Study**	**Age range** (years)	**Vaccines**	**Number of subjects exposed**	**Planned duration of study (**days) for each subject
USA	V59P13 Phase 3	11-55	MenACWY[a]	2649	180
			Menactra	875	
Argentina / Colombia	V59P17 Phase 3	19-65	MenACWY[a]	1600[d] (19-55 years); 217[d] (56-65 years)	180
			Menactra	889[d] (19-55 years)	
			Menomune	109 (56-65 years)	
Costa Rica	V59P18 Phase 3	11-18	MenACWY[a]+Tdap[c]+ HPV	540	211
			MenACWY[a] followed by HPV	541	271
			Tdap[c] followed by ACWY	539	
USA	V59P6 Phase 2	11-17	MenACWY[a]	151	360
			MenACWY adjuvanted	164	
			Menomune	209	
Europe (Italy)	V59P11 Phase 3	11-25	MenACWY[a]	357	181
			Tdap[c]+ MenACWY[a]	359	
			Tdap[c]	353	

[a]non-adjuvanted final MenACWY formulation

[c]Tdap in V59P11 was the licensed European Union formulation' Tdap in VP59P18 was the formulation licensed in the USA.

[d]Twenty subjects were exposed but did not provide safety information; 12 of the 1600 MenACWY subjects 19-55 years of age, one of the 217 MenACWY subjects 56-65 years of age, and 7 of the 889 Menactra subjects 19-55 years of age.

Table 7. Overview of reactogenicity: Total MenACWY versus Menactra, pooled Age Groups and Pooled studies.

Solicited reaction	**Category**	**Total MenACWY** N=6185 N (%)	**Total Menactra** N=1757 N (%)
Any reaction	Any	3966 (64)	1146 (65)
	severe	507 (8)	110 (6)
Local	Any	2934 (47)	906 (52)
	Severe[a, b]	225 (4)	54 (3)
Systemic	Any	2740 (44)	725 (41)
	severe[a, b]	355 (6)	70 (4)
Other	Any[c]	1180 (19)	345 (20)

Cell entries are number (%) o subjects exposed with at least one local, systemic or other reaction.

[a]Most severe across all injections.

[b]Severe local reaction=severe erythema, pain, or induration >50 mm: severe fever = ≥39C.

[c]Any other reactions=stayed at home; analgesic/antipyretic medication use.

Table 8. Summary of individual signs of reactogenicity: total MenACWY compared with Menactra in pooled studies, Days 1 to 7, pooled age groups.

Reactions	Category	Total MenACWY N=6185 n (%)	Menactra N=1757 n (%)
Local reactions			
Pain	Any	2524 (41)	816 (46)
	Severe	100 (2)	36 (2)
Erythema	Any	926 (15)	231 (13)
	>50 mm	97 (2)	17 (1)
Induration	Any	775 (13)	203 (12)
	>50 mm	86 (1)	15 (1)
Systemic reactions			
Chills	Any	545 (9)	120 (7)
	Severe	53 (1)	6 (<1)
Nausea	Any	625 (10)	142 (8)
	Severe	47 (1)	9 (1)
Malaise	Any	961 (16)	285 (16)
	Severe	107 (2)	22 (1)
Myalgia	Any	1130 (18)	280 (16)
	Severe	104 (2)	17 (1)
Arthralgia	Any	580 (9)	130 (7)
	Severe	61 (1)	10 (1)
Headache	Any	1881 (30)	491 (28)
	Severe	203 (3)	38 (2)
Rash	Any	160 (3)	42 (2)
Fever	38-38.9°C	125 (2)	27 (2)
	39-39.9°C	30 (<1)	8 (<1)
	≥40°C	6 (<1)	2 ()<1
Other reactions			
Stayed at home	Yes	268 (4)	63 (4)
Analgesic/antipyretic use	Yes	1066 (17)	326 (19)

Table 9. Overview of unsolicited adverse events: comparing total ACWY to Menactra in pooled studies and pooled age groups.

Time	Overview of unsolicited adverse evens	Total MenACWY N or n (%)	Menactra N or n (%)
Month 1	Total exposed N	6185	1757
	Any AE	1076 (17)	356 (20)
	Any severe AE	59 (1)	16 91)
	Possibly/probably related AE	357 (6)	128 (7)
	Severe possibly/probably related AE	21 (<1)	5 (<1)
	Any SAE	7 (<1)	4 (<1)
	Possibly/probably related SAE	0	0
	Death	0	0
Month 2	Total exposed N	5068	1746
	Any AE	460 (9)	134 (8)
	Any severe AE	42 91)	14 (1)
	Possibly/probably related AE	3 (<1)	1 (<1)
	Severe possibly/probably related AE	0	0
	Any SAE	31 91)	10 (1)
	Possibly/probably related SAE	1 (<1)	0
	Death	0	0

SAE=serious adverse event.

Table 10. Summary of severe unsolicited adverse events within one month after vaccination: Total MenACWY compared with Menactra in pooled studies (shown as incidence, N).

Unsolicited adverse events		Total MenACWY N=6185	Menactra N=1757
MedDRA system Organ class	**MedDRA preferred term**		
Any severe AE		59	16
Gastrointestinal disorders	Nausea	5	1
General disorders and administration conditions	Injection site pain	3	0
	Malaise	6	1
Infections and manifestations	Pharyngitis streptococcal	2	0
Musculoskeletal, connective tissue & bone disorders	Arthralgia	3	2
	Myalgia	3	1
Nervous system disorders	Headache	14	4
	Migraine	3	1
Psychiatric disorders	Depression	3	0

Criterion for inclusion in this table: ≥2 or more subjects in the total MenACWY group. N=number of subjects (incidence).

Table 11. Summary of probably or possibly related unsolicited adverse events within 1 month after vaccination: total MenACWY compared with Menactra in pooled age groups and pooled studies and sorted by decreasing frequency.

Unsolicited AE	**Total Men ACWY (N=6185)**	**Menactra (N=1757)**
Headache	62	20
Malaise	34	5
Injection site erythema	32	2
Injection site pain	28	8
Injection site pruritus	25	5
Myalgia	23	7
Nausea	23	3
Injection site induration	21	1
Arthralgia	18	11
Erythema	14	4
Diarrhoea	13	5
Lymphadenopathy	13	2
Rash	13	5
Nasopharyngitis	12	5
Dizziness	10	12
Pharyngolaryngeal pain	10	5
induration	10	2

Criterion for inclusion in this table: ≥10 subjects in the total MenACWY group.

Table 12. Summary of probably or possibly related unsolicited adverse events by MedDRA system organ class: Total MenACWY across age groups (% shown in brackets).

Unsolicited Adverse Evens: MedDRA system organ class	**Total MenACWY Age groups**			**Total MenACWY** N=6185	**Menactra** N=177
	11-18 N=3579	**19-34** N=1145	**35-55** N=1461		
Any AE	147 (4)	87 (8)	131 (9)	356 (6)	130 (7)
General disorders & administrative site conditions	71 (2)	32 (3)	65 (4)	168 (3)	36 92)
Nervous system disorders	31 (1)	33 (3)	30 (2)	94 (2)	42 92)
Gastrointestinal disorders	27 (1)	18 (2)	9 (1)	54 (1)	21 (1)
Musculoskeletal, connective issue disorders and bone disorders	17 (<1)	7 (1)	26 (2)	50 (1)	21 (1)
Infections & infestations	11 (<1)	10	17 (1)	38 (1)	14 (1)
Skin and subcutaneous disorders	10 (<1)	6	16 91)	32 (1)	16 (1)

The overall incidence of solicited reactogenic events was similar between groups that received Men ACWY conjugate vaccine either alone or with a concomitant vaccine and those that received Menactra. Across all studies there was a marginally higher percentage of

Menactra subjects with at least one solicited local reaction compared with Men ACWY conjugate vaccine subjects. Conversely there was a marginally higher percentage of Men ACWY conjugate vaccine subjects with a systemic reaction when compared with the Menactra subjects. The overall rate of any severe solicited local or systemic reactions within the first seven days after vaccination was similar between both groups (8% Men ACWY conjugate versus 6% Menactra). Overall the reactogenicity after Men ACWY conjugate vaccine given alone was lower than after tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine. The percentage of subjects reporting at least one solicited adverse event of Men ACWY conjugate vaccine subjects was 67%, 65% and 56% for 11 to 18 year olds, 19 to 34 year olds and 35 to 55 year old age groups respectively. In subjects that received Boostrix and Gardasil vaccines when administered concomitantly with Men ACWY conjugate vaccine, the incidence of systemic reactogenic events was slightly higher than when Men ACWY conjugate vaccine was given alone.

The administration of Boostrix one month before Men ACWY conjugate vaccine did not change the incidence or severity of reactogenic events after Men ACWY conjugate vaccine alone. At one month following vaccination, unsolicited adverse events were reported in approximately 17% of Men ACWY conjugate vaccine and 20% of Menactra subjects, and only 1% of subjects in each group had unsolicited adverse events considered severe. The only unsolicited adverse event reported in more than 1% of subjects during month one post vaccination was headache (2% in each vaccine group). In total 6% of Men ACWY conjugate vaccine subjects and 7% of Menactra subjects reported unsolicited adverse events assessed as possibly or probably related to the vaccine within month one post vaccination. During month 2 to 6 after vaccination, unsolicited adverse events were reported in 8% of Men ACWY conjugate vaccine subjects and 9% of Menactra subjects. Only 1% of subjects had a serious adverse event at any time during the study in both the Men ACWY conjugate vaccine and Menactra groups. Less than 1% of subjects had a serious adverse event during month one. Serious adverse events during month 2 to 6 occurred of incidences at 1% or less.

Adverse Events

- In all studies in the Men ACWY conjugate vaccine development program, solicited adverse events were evaluated on the day of vaccination through 7 days after vaccination. Each type of solicited adverse event was summarised by subjects by vaccine group and age group for each study and pooled across studies. The percentages of Men ACWY conjugate vaccine and Menactra subjects who experienced at least one solicited adverse event within 7 days after vaccination were similar (64% versus 65%) as were the percentages of subjects with any severe reaction (8% versus 6%) for Men ACWY conjugate vaccine versus Menactra.
- In pooled studies and in pooled age groups, the most common local reaction was injection site pain for both vaccine groups (Men ACWY conjugate vaccine 41% versus Menactra 46%). Erythema (15% and 13% respectively) and induration (13% and 12% respectively) were reported less frequently.
- The most common systemic reactions in total Men ACWY conjugate vaccine and Menactra vaccine groups were headache (30% versus 28%), myalgia (18% versus 16%), malaise (16% in both vaccine groups), nausea (10% and 8%) and chills (9% and 7%). Across the two vaccine groups severe systemic reactions were recorded by less than 1-3%.
- In the total Men ACWY and Menactra comparison in pooled studies and pooled aged groups, the most common local reaction during 7 days after vaccination was injection site

pain (41% versus 46% for Menactra). Severe pain was reported infrequently (2% for both vaccines). With regard to unsolicited adverse events, the incidence of unsolicited adverse events was slightly lower for total Men ACWY conjugate vaccine (17%) than for Menactra (20%) pooled across studies and age groups. Any adverse events that were severe in intensity were reported by 1% in Men ACWY conjugate vaccine and Menactra subjects.

Serious Adverse Events

- As of 15th February 2008 there were 292 serious adverse events reported to the Novartis Vaccine Pharmaco-vigilance database in subjects who received any formulation of Men ACWY conjugate vaccine. Less than 1% of both the total of Men ACWY conjugate vaccine and Menactra groups reported at least one serious adverse event from vaccination day through the 6 month follow up in the 5 studies supporting the proposed indication. 7 subjects reported serious adverse events during month 1, and 31 subjects reported serious adverse events during month 2 to 6. All the individual serious adverse events occurred in incidences of less than 1% and there were no clinically meaningful differences in serious adverse events incidence between total Men ACWY conjugate vaccine and Menactra groups.
- Serious adverse events reported by more than one total meningococcal ACWY conjugate vaccine subject each were spontaneous abortion (4 subjects), appendicitis and road traffic accidents (3 subjects each) and suicide attempt (2 subjects). No deaths occurred among subjects within the proposed indication of 11 to 55 years although two deaths occurred in vaccinees outside of the proposed indication, neither of which was judged as related to meningococcal ACWY conjugate vaccine.

Comments on Safety

- Information on safety was evaluated in 3,579 adolescents (11 to 18 years) and 2,606 adults (aged 19 to 55 years) in three pivotal studies (V59 P13, V59 P17, and V59 P18) and two supportive studies (V59 P6 and V59 P11). These studies were identified as utilising the final formulation of Men ACWY in the proposed target population.
- V59 P13 has previously been described in the section on immunogenicity. In addition to immunogenicity objectives, this study was also designed to assess non-inferiority with regard to the differerence between Men ACWY and Menactra in the percentage of subjects with a severe systemic reaction. This non-inferiority criteria was met, with the difference being 1% (95% CI [-1, 2]). Overall reactogenicity rates were similar between Men ACWY and Menactra (62% versus 67% reporting at least 1 event respectively) and severe local and systemic reactions were reported by 1% to 2% more Men ACWY than Menactra subjects. A total of 2,649 subjects received Men ACWY in this study.
- V59 P17 was designed to assess safety of Men ACWY compared to Menactra. This study was also designed to assess non-inferiority with regard to the difference between Men ACWY and Menactra in the percentage of subjects with a severe systemic reaction. This criteria was met with the difference being 1% (95% confidence interval [-1, 3]). Overall reactogenicity and severe local reactions were also comparable between both groups. A total of 1,588 subjects received Men ACWY in this study
- V59 P18 was designed to assess safety of Men ACWY administered concomitantly with Boostrix and Gardasil vaccines, as well as Men ACWY administered 1 month after Boostrix. This study is ongoing, but safety results suggested that Men ACWY was less reactogenic than Boostrix, and the reactogenicity profile of Men ACWY was similar

whether given alone, concomitantly with Boostrix and Gardasil, or sequentially after Boostrix. Safety data was collected for 1,620 subjects.

- V59 P6 has previously been described in the section on immunogenicity. This study compared safety of Men ACWY relative to Menomune (a polysaccharide meningococcal ACWY vaccine) in adolescents. No safety issues were identified with either vaccine, although Men ACWY was noted to be more reactogenic than Menomune. 315 subjects received Menomune in this study.
- V59 P11 has previously been described in the section of immunogenicity. This study assessed safety of Men ACWY with and without Boostrix, versus Boostrix alone. Men ACWY was noted to be less reactogenic than Boostrix.
- In addition to these individual studies, information on safety was also provided from pooled data for the five studies described above. This included a total of 6,185 subjects with Men ACWY being administered to 3,579 adolescents (11 to 18 years) and 2,606 adults (19 to 55 years). This compared to 1,757subjects who received Menactra, 209 who received Menomune, and 892 receiving Boostrix.
- While there were significant methodological differences between the studies contributing to the pooled data, the overall incidence of solicited reactogenic events was similar between groups that received Men ACWY and Menactra. There was marginally higher percentage of Menactra subjects with at least 1 solicited local reaction compared with Men ACWY, although this trend was reversed for systemic reactions. The percentage of subjects with each type of reaction differed by only 1 or 2% between the two vaccine groups with the exception of injection site pain, which was reported for 5% more Menactra subjects. Men ACWY local reactogenicity was not impacted when given with or after other routinely administered vaccines for this age group (Boostrix and Gardasil).
- With regard to severe adverse events, no severe adverse events in Men ACWY subjects exceeded 1%. The most frequently reported severe adverse events in the Men ACWY groups were headache, malaise and nausea during the first month after vaccination. There were no clinically meaningful differences between the Men ACWY or Menactra groups. No deaths were reported during or after the study period in the five studies included in the pooled safety data. There were 2 deaths in groups who received Men ACWY outside of the proposed indication (V59 P14, V59 P17). These were felt to be unrelated to the vaccine.
- Only limited safety information was provided with regard to pregnancy. A total of 34 women were identified who became pregnant during the 6 month follow up period. Of these, twenty eight received Men ACWY and 6 received Menactra. From these subjects, there have been four miscarriages, five therapeutic abortions and one congenital deformity. These outcomes were felt not to be related to study vaccines.

Clinical Summary and Conclusions

Three phase 2 clinical studies were performed to assess clinical pharmacology in this application, particularly with regard to selection of the final formulation. Particular factors to be considered were the specific composition with regard to the specific serotypes (A, C, W-135 and Y), as well as the presence or absence of adjuvant (aluminium phosphate, 0.6 mg/mL as Al^{3+}). These studies were all conducted in toddlers or infants, which was different from the proposed age range for the vaccine. This also made interpretations difficult, due to possible factors such as maternal antibodies. Despite this, the studies suggested that the immune response induced by 10µg antigen of groups C, W and Y were not consistently

higher than 5 µg antigen of the same serogroups. The immune response to 10 µg antigen of group A was noted to be consistently higher than 5 µg antigen. As such, it was decided to proceed with a vaccine containing 10 µg/5 µg/5 µg/5 µg of antigen to serogroups A, C, W and Y respectively. There were no significant differences in immunogenicity between the vaccines containing adjuvant and those not containing adjuvant. While these results were obtained in studies involving toddlers, the immunogenicity suggested in these studies was consistent with the results from the phase 3 clinical studies.

Information on immunogenicity was provided by 4 pivotal clinical studies. Two studies compared the immunogenicity of Menveo against comparators. V59 P13 compared Menveo with Menactra (meningococcal ACWY conjugate vaccine), while V59 P6 compared Menveo with Menomune (meningococcal ACWY polysaccharide vaccine). Menomune is registered for use in Australia, while Menactra is only registered in the USA and Canada. These studies were designed to assess non-inferiority of Menveo against the comparator vaccine. In study V59 P13, Menveo was noted to be highly immunogenic with GMTs against the respective serogroups being 29 (24, 25), 59 (48, 73), 87 (74, 102) and 51 (42, 61) against serogroups A, C, W-135 and Y one month post vaccination. Percentage of seroresponders ≥ 1:8 was noted to be 75% (73, 78), 84% (82, 86), 96% (95, 97) and 88% (85, 90) against serogroups A, C, W-135 and Y. Non inferiority was demonstrated against Menactra, as well as lot-to-lot consistency in this study. V59 P6 demonstrated similar non-inferiority against Menomune.

The other 2 pivotal clinical studies, V59 P18 and V59 P11, were non-interference studies that evaluated concomitant and sequential vaccination with Boostrix and Gardasil in adolescents (V59 P18) and Boostrix in 11 to 25 year olds (V59 P11). Study V59 P18 was ongoing, with limited information available on the interaction with Gardasil. There was no evidence of interaction with Boostrix. V59 P18 was designed to assess non-inferiority in terms of the response to Menveo and this was demonstrated. Study V59 P11 was designed to assess non-inferiority in terms of the response to Boostrix, with the response to Menveo being limited to descriptive analyses only.

A large number of supporting studies were provided that either used a different formulation, or involved a different target population to that proposed. All studies suggested that Menveo was immunogenic for serogroups A, C, W-135 and Y. Two studies compared immunogenicity of Menveo against Menjugate, a meningococcal C conjugate vaccine currently registered in Australia. These studies were difficult to interpret, as they involved infants and toddlers receiving at least 2 doses of Menveo. In study V59 P5, immunogenicity (hSBA ≥ 1:4) against serogroup C was significantly higher at 1 month in the Menjugate group (98%), compared to 84% / 86% in the Menveo groups with and without adjuvant. Both vaccines were immunogenic.

Study V59 P6 also provided some information with regard to persistence of the immune response at 1 year following a single injection of Menveo in adolescents. This was compared to persistence of immune response following a single injection of Menomune-a polysaccharide quadrivalent vaccine. At 1 year after vaccinations, persistence of bacterial antibodies was maintained for all 4 serogroups with percentage of subjects with titres ≥ 1:4 and titres ≥ 1:8 in the Menveo group significantly higher than in the Menomune group against serogroups C, W and Y and similar for serogroup A (although less for percentage of subjects with hSBA titres ≥ 1:4 (p=0.43). No information on requirement for boosters was provided.

Safety was assessed in three pivotal studies (V59 P13, V59 P17 and V59 P18), as well as by assessment of pooled data from all studies using the final formulation on the proposed target population. This involved a total of 6,185 subjects who received Menveo. Studies V59 P13

and V59 P17 were both designed to assess non-inferiority between Menveo and Menactra in terms of percentage of subjects with a severe systemic reaction. This was demonstrated although interpretation was difficult given the small percentage of subjects with severe systemic reaction in both groups. In terms of pooled data, reactogenicity and adverse reactions were noted to be similar or better than comparable vaccines in most cases. The most common side effects were noted to be headache, nausea, malaise, injection site pain, injection site erythema (≤50mm) and injection site induration (≤50mm). No deaths were reported in study subjects for the proposed formulation or target population, although 2 unrelated deaths occurred in relation to other studies.

In summary, sufficient information was provided to indicate that Menveo is immunogenic and safe for the proposed indication in Australia. While much of the pivotal data relies on comparison with Menactra, a meningococcal ACWY conjugate vaccine, which is not registered in Australia, it has been approved by the FDA for use in the USA and by Health Canada. Clinical studies have also indicated levels of immune response that are accepted as correlating with protection against the respective serogroups.

Also of note is that the proposed target population is adolescents (11 to 18 years) and adults (19 to 55 years). Currently the recommendation for meningococcal C conjugate vaccine in Australia is for a single dose at 12 months, with the rationale being to cover both peaks of meningococcal disease, young children less than 5 years of age, and adolescents from 15 to 24 years of age. This means that Menveo is unlikely to replace meningococcal C conjugate vaccine in the childhood immunisation program, although potentially it could be used for 'catch-up' vaccination in the adolescent group. In addition, most meningococcal disease in Australia is caused by serogroups B (73%) and serogroup C (14.5%) with few cases of serogroups A, W-135 and Y.

The use of Menveo as a travel vaccine also raises some issues. Information provided in the submission indicates that Menveo compares favourably to polysaccharide quadrivalent vaccines (such as Menomune-a) in terms of both immunogenicity and safety. However, no information is provided in terms of possible interaction with other commonly used travel vaccines, as well as any requirement for boosting.

While the above factors should be considered, this application provided sufficient information to support registration in Australia for the proposed indication.

Postmarketing experience

No post marketing surveillance data was provided, as Meningococcal ACWY conjugate vaccine has not been marketed in any region of the world. No post marketing data on either equivalent vaccines (that is, Menactra) or single serogroup conjugate vaccines (that is, Menjugate) was provided.

Comments on the proposed product information

The proposed product information was clearly set out, and easy to understand. With regard to the section on *Interaction with other Medicines*, no comment has been made about interactions with travel vaccines (such as Typhoid and Hepatitis A/B). Experience with this should be stated, given the other potential use for this vaccine.

V. Pharmacovigilance Findings

There was no Risk Management Plan submitted with this application as it was not a requirement at the time of submission.

VI. Overall Conclusion and Risk/Benefit Assessment

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

Quality

A number of issues were identified and referred to the sponsor during the evaluation, and the satisfactory resolutions have been provided by the sponsor for all issues except the issue relating to the naming of the product and the active ingredients. The nomenclature for the active ingredients and full trade name is currently under negotiation, and a satisfactory resolution is expected.

The quality data has been reviewed by the Pharmaceutical Subcommittee (PSC), and the PSC has no objection on quality and pharmaceutics grounds to the registration of Menveo provided that all outstanding issues are addressed to the satisfaction of the TGA. The PSC considered that the instructions for reconstitution in the Product Information should be improved.

Overall, the recommendation from the Quality evaluation is that the application to register Menveo should be approved provided that

- the naming of the product and drug substances is satisfactorily resolved

and (as is usual for a biological product)

- for each batch of vaccine imported into Australia, TGA Office of Laboratories and Scientific Services (OLSS) should be provided with-:
  - Complete protocol of manufacture and quality control testing of the batch.
  - 30 doses of the vaccine in the final container.
  - Evidence of a Certificate of Release for each batch from the relevant National Control Authority.
  - Documentation including appropriate temperature monitors to show that the recommended storage conditions were maintained during the transportation of the vaccine to Australia.
  - Reference materials and SOP's necessary for the testing of the vaccine as requested by OLSS.

Nonclinical

There are no nonclinical concerns on the capacity for Menveo to induce a tetravalent (MenA, C, W-135 and Y) immune response based on the submitted non-clinical data. Reproductive and fetal toxicity studies were performed in rabbits vaccinated with MenACWY (or adjuvant control) and no vaccine-associated toxicity was detected in either the maternal rabbits or fetuses or kits. No carcinogenicity or genotoxicity studies were submitted. No nonclinical protective efficacy studies were conducted due to the lack of suitable animal models of *N. meningitidis* infection.

The analysis of the non-clinical data and the literature suggests that awareness is required on the activation of eosinophils post-vaccination, as eosinophil-mediated hypersensitivity complications in humans receiving meningococcal vaccines have been observed and reported in the biomedical literature.

The review of the submitted literature raises the concern regarding the inability to include serogroup B antigen in the vaccine formulations, and the possible risk of Guillain-Barre syndrome (GBS) post-vaccination.

Clinical

The clinical data consists of three earlier studies assessing the optimal vaccine dose and formulation, four main studies assessing immunogenicity and safety, one additional safety study, and a number of supportive studies.

Studies evaluating vaccine dose and formulation

Three Phase II studies (V59P2, V59P7, and V59P4) were conducted to determine:

1. The effect of different doses (2.5 µg to 10 µg) of each serogroup antigen on the immune response; and
2. The need for an adjuvant (aluminium phosphate, 0.6 mg/mL as Al^{3+}) in the formulation of the candidate vaccine.

These studies suggested that there was no significant difference in immunogenicity between study subjects who received the vaccine with or without the Al^{3+} adjuvant, and the immune responses induced by 10µg antigen of groups C, W and Y were not consistently higher than 5 µg antigen of the same serogroups. The immune response to 10 µg antigen of group A was noted to be consistently higher than 5 µg antigen. It was therefore decided to proceed with a non-adjuvanted vaccine containing 10 µg/ 5 µg/ 5 µg/ 5 µg of antigen to serogroups A, C, W and Y respectively. It is noted that these studies were all conducted in toddlers or infants, which was different from the proposed age range for the vaccine. However, the immunogenicity suggested in these studies was consistent with the results from the Phase III studies.

Immunogenicity / efficacy evaluation

Two pivotal (V59P13 and V59P18) and two supportive (V59P6 and V59P11) studies are submitted and these studies assessed the immunogenicity of MenACWY. The efficacy of MenACWY is inferred from the immunogenicity in terms of serum bactericidal antibodies. Seminal data collated among military recruits in the 1960s defined a protective hSBA (human serum bactericidal assay) titer threshold of≥ 1:4 titer a gainst invasive disease (Goldschneider I *et al.*, 1969a)[12]. Based on intrinsic characteristics of the assay which uses a starting dilution of 1:4, a more conservative threshold of hSBA titer ≥ 1:8 has been used in the MenACWY development program.

The following endpoints were used in the submitted studies:

- Seroresponse one month after vaccination. Seroresponse was defined as:
    a) for a subject with a pre-vaccination human serum bactericidal assay (hSBA) titer < 1:4 at baseline (that is, seronegative), seroresponse was defined as a post-vaccination hSBA titer ≥ 1:8;
    b) for a subject with a pre-vaccination hSBA titer ≥ 1:4 (that is, seropositive), seroresponse was defined as a post-vaccination hSBA titer of at least four times the pre-vaccination titer.
- hSBA titer ≥ 1:8;
- hSBA titer ≥ 1:4;
- hSBA Geometric Mean Titers (GMTs);

[12] Goldschneider et al (1969). Human immunity to the meningococcus. I. The role of humoral antibodies. *J. Exp. Med.* 129: 1327-1348.

V59 P13 is the most important study in this submission. It was a Phase III randomised observer blind controlled multicentre study. The primary objectives of the study are:

1) To establish clinical lot-to-lot consistency between three lots of MenACWY with respect to hSBA GMTs, in adolescents aged 11 to18 years.
2) To demonstrate non-inferiority of MenACWY compared with Menactra, as measured by the percentage of subjects with seroresponse in adolescents aged 11 to 18 years.
3) To demonstrate non-inferiority of MenACWY relative to Menactra, as measured by the percentage of subjects with seroresponse in adults aged 19 to 55 years.

Menactra is a conjugate meningococcal vaccine containing serogroup A, C, W, Y, and it is marketed in the United States and Canada.

A total of 3,539 subjects 11 to 55 years of age were randomised at a 1:1:1:1 ratio to one of four vaccine groups: MenACWY lot 1, lot 2, lot 3 or Menactra. A total of 3539 subjects were enrolled (2663 MenACWY subjects and 876 Menactra subjects), and 3393 were included in the Per Protocol population (2549 MenACWY subjects and 844 Menactra subjects).

The immunogenicity of the three lots of MenACWY was considered equivalent if for each serogroup and each pair of vaccine lots, the 2-sided 95% CI of the GMT ratio one month after the vaccination was within the interval 0.50- 2.0,

Seroresponse was the primary endpoint to assess the non-inferiority. The assessment of non-inferiority was based on the lower limit of the two-sided 95% confidence interval (CI) for the difference in the percentages of seroresponders between the two vaccine groups (MenACWY – Menactra). If the CI was entirely to the right of -10%, then the non-inferiority can be concluded. In addition, if the CI was entirely to the right of 0%, then MenACWY was considered to have a statistically superior immune response to Menactra with significance at the 5% level ($P < .05$). This non-inferiority, followed by a superiority testing procedure, was explicitly stated in the V59P13 study protocol.

The study results showed that the consistency in immune response was demonstrated among the three vaccine lots for all four serogroups (that is, for all 3 pair wise comparisons the two sided 95% confidence interval (CI) of the ratio of the GMT's was within the interval 0.5, 2.0), and the seroresponse to MenACWY was non-inferior to that of Menactra for all four serogroups in both the 11 to 18 and the 19 to 55 age groups (that is, the lower limit of the two sided 95% CI was greater than -10%). In addition, seroresponse to MenACWY was shown to be superior (two sided 95% CI was greater than 0%) to that of Menactra for serogroups A, W and Y in the 11 to 18 age group and for serogroups C, W and Y in the 19 to 55 age group.

V59 P18 was an open-label randomised controlled Phase III study to assess concomitant and sequential MenACWY vaccination with routine immunization. The study assessed the immune response to MenACWY with and without Boostrix (Tdap) and Gardasil (HPV) vaccines. Subjects were healthy adolescents (11-18 years old) who were randomised to receive either MenACWY concomitantly with Tdap and Gardasil, MenACWY at Day 1 with Tdap on Day 31, or Tdap at Day 1 followed by MenACWY on Day 31. The primary objectives were to demonstrate non-inferiority in the percentage of seroresponders between the first two groups, to demonstrate non-inferiority between the latter two groups in the percentage of seroresponders, and to demonstrate non-inferiority of Tdap when administered concomitantly and alone in terms of seroresponse against specific diphtheria, tetanus and pertussis antigens. This study is ongoing, and no information was available on the interaction with Gardasil.

A total of 1620 subjects were enrolled, and 1454 and 1441 subjects were included in the Per Protocol populations for the MenACWY and Tdap immunogenicity analyses, respectively. The immunogenicity results showed that

- Noninferiority was demonstrated in all serogroups for concomitant use of MenACWY with Tdap and HPV vaccine versus MenACWY alone
- Noninferiority was demonstrated for serogroups A, C or Y, but not W, for seroresponse rates for MenACWY administered one month after Tdap versus MenACWY alone at Day 1.
- Immunogenicity of Tdap against tetanus and diphtheria was noninferior when given concomitantly with MenACWY compared with Tdap alone
- Immunogenicity of Tdap against pertussis was noninferior when given concomitantly with MenACWY compared with Tdap alone for PT antigen, but not for the filamentous hemagglutinin antigen (FHA) or for the pertactin antigen (PRN).

V59 P6 was a Phase II randomised single blind controlled multicentre study. The study compared the safety and immunogenicity of MenACWY (with or without Al^{3+} adjuvant) with Menomune, a meningococcal ACWY polysaccharide vaccine licensed in Australia. The study was conducted in healthy adolescents 11 to 17 years of age. A total of 148 MenACWY Ad- subjects and 179 Menomune subjects were included in the Per Protocol analysis.

The study subjects received one injection of MenACWY or Menomune. Immune responses were measured at 1 month and at 1 year post-vaccination. Results are presented for the MenACWY nonadjuvanted formulation only. It should be noted that the primary endpoint to assess non-inferiority was set at hSBA titer≥ 1:4 in this study. It was only in later trials that the more conservative primary endpoint of seroresponse was adopted. Although not a pre-specified study objective, for consistency with the other studies, non-inferiority in terms of hSBA seroresponse, percentages with hSBA titer≥ 1:8, and hSBA GMTs for MenACWY to Menomune were assessed post-hoc, and are provided as supportive data. The post-hoc analysis showed that at 1 month post vaccination:

- MenACWY was noninferior to Menomune for all four serogroups, based on seroresponse, hSBA titer ≥1:8 and GMTs.
- MenACWY was superior to Menomune for all serogroups, based on seroresponse and GMTs.
- MenACWY was superior to Menomune for serogroups A, C and Y in the percentage of subjects with post vaccination hSBA titer≥1:8.

Study V59 P6 also provided information with regard to the persistence of the immune response at one year following a single injection of MenACWY in adolescents. This was compared to Menomune. At one year post vaccination:

- Persistence of hSBA was maintained for all four serogroups. The percentages of subjects with hSBA titer≥ 1:4 and ≥ 1:8 in the MenACWY group were still significantly higher than in the Menomune group against serogroups C, W, and Y. For serogroup A, the percentage of subjects with hSBA ≥ 1:8 was similar between the two vaccine groups, while the percentage of subjects with hSBA≥ 1:4 was significantly lower in the MenACWY group (P=.043).

- The hSBA GMTs were still significantly higher in the MenACWY group than in the Menomune group against serogroups W and Y, while for serogroups A and C they were similar between the two vaccine groups.

V59 P11 was a Phase III randomized, observer-blind, noninterference, controlled, multicenter study conducted in Italy in subjects aged 11 to 25 years. Subjects were randomly assigned at a 1:1:1 ratio to receive one injection of:

- Tdap (Boostrix) concomitantly with one injection of MenACWY;
- Tdap concomitantly with saline placebo; or
- MenACWY concomitantly with saline placebo.

The primary objective was to demonstrate non-inferiority of Tdap given concomitantly with MenACWY compared to Tdap given concomitantly with saline placebo. The secondary objective was to evaluate immune response of MenACWY administered concomitantly with Tdap versus MenACWY administered concomitantly with saline placebo. Only the result of the secondary objective is presented here.

Of the 1072 subjects enrolled, 718 subjects were randomized to receive MenACWY (361 subjects in the MenACWY + Tdap group and 357 in the MenACWY + saline placebo group). Of these 718 subjects, 701 were included in the Per Protocol analysis. The immune responses induced by MenACWY given concomitantly with Tdap or with saline were assessed in a randomly selected subset of 245 subjects by descriptive analysis only. The results showed:

The immune responses against any serogroup were similar when MenACWY was given with Tdap and when MenACWY was given with saline placebo.

- The percentages of seroresponders and the percentages of subjects with hSBA titer ≥ 1:8 and ≥ 1:4 were similar for all serogroups when MenACWY was administered concomitantly with Tdap or with saline placebo.
- hSBA GMTs were similar for serogroups C, W, and Y in all vaccine groups but slightly lower for serogroup A when MenACWY was administered with Tdap than when it was administered with saline placebo.

Other studies: In addition to the above four studies, a large number of supporting studies were provided. The evaluator considers that the results of these studies are difficult to interpret due to the fact that different formulations and different target population were employed in these studies. Of particular note is study V59P5 which involved the comparison to Menjugate, a serogroup C conjugate meningococcal vaccine registered in Australia. Study V59 P5 was a Phase II open-label, randomised controlled study designed to assess scheduling of two or three doses of MenACWY with concomitant infant routine vaccinations. Subjects were healthy infants of 2 months of age. One of the secondary immunogenicity objectives was to compare the immunogenicity of MenACWY with or without adjuvant (containing 5 µg of MenC oligosaccharide) with that of Menjugate (containing 10µg of MenC oligosaccharide) when administered in a two dose regimen, as measured by hSBA ≥ 1:4 and hSBA ≥ 1:8 against serogroup C. The comparison was limited to descriptive analysis only. The results showed that the percentage of subjects with hSBA titers ≥ 1:4 in the Menjugate group was greater (98%) at 1 month after the second of the two primary doses compared with the two-dose of MenACWY Ad+ and Ad- groups (84% in the Ad+ group and 86% in the Ad- group). Similar results were obtained when the hSBA titers ≥ 1:8 against serogroup C was used. The percentage of subjects with hSBA titers ≥ 1:8 was greater in the Menjugate group (98%) compared with the MenACWY groups (83% in the Ad+ group and 82% in the Ad- group).

Safety evaluation

Safety profile of MenACWY was evaluated in three pivotal studies (V59 P13, V59 P17, and V59 P18) and two supportive studies (V59 P6 and V59 P11). These studies were identified as utilising the final formulation of MenACWY in the proposed target population (11-55 years of age).

V59 P13 contributed the safety data for 2649 MenACWY subjects. The study assessed the non-inferiority in terms of the difference between MenACWY and Menactra in the percentage of subjects with a severe systemic reaction. This non-inferiority criterion was met, with the difference being 1% (95% CI [-1, 2]). Overall rates of reactogenicity were similar between MenACWY and Menactra (62% versus 67% reporting at least 1 event respectively) and severe local and systemic reactions were reported by 1% to 2% more MenACWY than Menactra subjects.

V59 P17 was a pivotal study designed to assess the safety of MenACWY relative to Menactra. Safety data were collected for 1588 MenACWY subjects aged 19 to 55 years. The study assessed non-inferiority of MenACWY relative to Menactra with regard to the difference in the percentage of subjects with a severe systemic reaction. This criterion was met with the difference being 1% (95% CI [-1, 3]). Overall the reactogenicity and severe local reactions were also comparable between the two vaccine groups.

V59 P18 assessed the safety of MenACWY administered concomitantly with Tdap (Boostrix) and Gardasil, as well as MenACWY administered 1 month after Tdap. The study was conducted in subjects aged 11 to 18 years, and safety data were collected for 1620 subjects (1081 received MenACWY). The results suggested that MenACWY was less reactogenic than Tdap, and the reactogenicity profile of MenACWY was similar whether given alone, concomitantly with Tdap and Gardasil, or sequentially after Tdap.

V59 P6 compared the safety of MenACWY relative to Menomune in adolescents. The study collected safety data on 315 MenACWY subjects (151 subjects with non-adjuvanted and 164 subjects with adjuvanted formulation). No safety issues were identified with either vaccine, although MenACWY was noted to be more reactogenic than Menomune. No serious adverse events (SAEs) related to the study vaccines were reported.

V59 P11 safety data for MenACWY was available for 716 Italian subjects aged 11 to 25 years. MenACWY was noted to be less reactogenic than the non-US formulation of Tdap.

Pooled safety data: in addition to the safety data from individual studies, safety information was also analysed from the pooled data form all five studies described above. This included a total of 6,185 subjects, including 3,579 adolescents (11 to 18 years) and 2,606 adults (19 to 55 years). This compared to 1,757subjects who received Menactra, 209 who received Menomune, and 892 receiving Boostrix.

While there were methodological differences between the five studies, the overall incidence of solicited reactogenic events was similar between groups that received MenACWY and Menactra. There was marginally higher percentage of Menactra subjects with at least 1 solicited local reaction compared with MenACWY, although this trend was reversed for systemic reactions. The percentage of subjects with each type of reaction differed by only 1 or 2% between the two vaccine groups with the exception of injection site pain, which was reported for 5% more Menactra subjects. MenACWY local reactogenicity was not impacted when given with or after other routinely administered vaccines for this age group (Boostrix and Gardasil).

With regard to SAEs, no SAEs in MenACWY subjects exceeded 1%. The most frequently reported SAEs in the MenACWY groups were headache, malaise and nausea during the first month after vaccination. No clinically meaningful differences were detected between MenACWY or Menactra groups. No deaths were reported during or after the study period in the pooled safety data. There were 2 deaths in groups who received MenACWY outside of the proposed indication. These were considered to be unrelated to the vaccine.

Only limited safety information was provided with regard to pregnancy. A total of 34 women were identified who became pregnant during the 6 month follow up period. Of these, 28 received MenACWY and 6 received Menactra. From these subjects, there have been four miscarriages, five therapeutic abortions and one congenital deformity. These outcomes were considered to be unrelated to the study vaccines.

Theoretical safety issues: A possible association between Guillain-Barré Syndrome (GBS) and receipt of Menactra was reported to the FDA in 2005, however, it is unclear if this represents an increased risk of GBS after vaccination in adolescents and there is insufficient data from the adult population to compare background rates of GBS. A known history of GBS is considered a contraindication to vaccine administration in the updated package insert. No cases of GBS were reported in the MenACWY clinical trials discussed above.

Evaluator's recommendation

The evaluator recommends approval of the application to register Menveo on the basis that sufficient information has been provided to indicate that Menveo is immunogenic and safe for the proposed indication in the proposed population.

Risk-Benefit Analysis

In the current application to register MenACWY, the immunogenicity of Menveo was compared with that of Menactra in Study V59P13 and was compared with Menomune in Study V59P6. The non-inferiority relative to Menactra was achieved for all four serogroups in adolescents and adults (11 to 55 years of age) and the non-inferiority relative to Menomune was achieved in adolescents 11 -17 years of age. The comparison to Menjugate was assessed as a secondary objective in a Phase II study (V59P5) and the percentage of subjects with hSBA$\geq$1:4 or 1:8 (against serogroup C) induced by MenACWY were lower than that induced by Menjugate.

The safety data from the 5 clinical studies involving 6185 subjects exposed to a single injection of MenACWY showed an acceptable safety profile.

Given the fact that the majority meningococcal diseases in Australia are caused by serogroups B and C, the main drawbacks for the use of MenACWY in Australia are the lack of protection to serogroup B, lower immunogenicity to serogroup C (compared to Menjugate), and lack of data in young children (high risk age group). Based on the data submitted, there appear to be a limited benefit of MenACWY over the currently available meningococcal vaccines. Menveo cannot be used as a routine childhood vaccine, and the use of this vaccine would be limited to people with an increased risk of acquiring meningococcal infection caused by serogroups A,C,W, and Y, such as travellers to countries recognized as having highly endemic and epidemic disease; control of epidemics of infection caused by *N. meningitidis* Groups A, C, Y and W-135 in confined communities; individuals at particular high risk of acquiring meningococcal infection, including persons with anatomic or functional asplenia; close contacts of persons with meningococcal disease due to groups A, C, Y and W-135, as an adjunct to appropriate chemoprophylaxis.

Proposed action

The Delegate proposed to approve the registration of Menveo for the following indication:

"Menveo is indicated for active immunization of adolescents (from 11 years of age) and adults for the prevention of invasive meningococcal disease caused by N. meningitides serogroups A, C, W-135 and Y.

Vaccination may be considered for the following individuals: Travellers to countries recognised as having highly endemic and epidemic disease; Control of epidemics of infection caused by Neisseria meningitidis Groups A, C, Y and W-135 in confined communities; Individuals at particular high risk of acquiring meningococcal infection, including persons with anatomic or functional asplenia; Close contacts of persons with meningococcal disease due to groups A, C, Y and W-135, as an adjunct to appropriate chemoprophylaxis."

The final approval is to be subject to

- Final resolution of the outstanding Quality issues
- Amendments of the PI to the satisfaction of the TGA
- Comply with the pharmacovigilance plan determined by the Office of Medicines Safety Monitoring (OMSM), TGA, including Routine Periodic Safety Update Report (PSURs) submissions following the registration.

The Advisory Committee on Prescription Medicines (ACPM) (formerly ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal to approve the application and proposed a modification to the indication (similar to that proposed by Novartis in their pre-ACPM response).

The ACPM recommends approval of the submission from Novartis Vaccines and Diagnostics Pty Ltd to register a new chemical entity meningococcal (Groups A, C, W-135 and Y) oligosaccharide CRM197 conjugate vaccine (MENVEO) powder and solvent solution for injection containing 10 µg of MenA oligosaccharide and 5 µg of MenC, MenW and MenY oligosaccharides / 0. 5 mL for the indication:

> *"Active immunisation of adolescents (from 11 years of age) and adults to prevent invasive disease caused by Neisseria meningitidis serogroups A, C, W-135 and Y. The use of this vaccine should be in accordance with official recommendations."*

In making this recommendation the ACPM did not express any concerns about immunogenicity but noted the raised eosinophil-mediated hypersensitivity and the incidence of Guillain-Barré syndrome. The lack of efficacy studies providing evidence about the combination with commonly used travel vaccines was also considered. The ACPM advised that approval for a wider indication would require a full comparative study against Meningococcal C conjugate vaccine. The ACPM advised that a list of potential target populations was not required and that the indication should refer to "in accordance with official recommendations". The ACPM also supported the Delegate's other recommended changes to the product information.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Menveo meningococcal conjugate vaccine 0.5 mL dose containing 10.0 µg of Meningococcal oligosaccharide - Group A and 16.7 µg Diphtheria CRM197 protein in a vial and 5.0 µg Meningococcal oligosaccharide - Group C; 5.0 µg Meningococcal oligosaccharide - Group W135; 5.0 µg Meningococcal Oligosaccharide - Group Y; and 16.0 µg Diphtheria CRM197 protein in a syringe, indicated for:

"Active immunisation of adolescents (from 11 years of age) and adults to prevent invasive disease caused by Neisseria meningitidis serogroups A, C, W-135 and Y. The use of this vaccine should be in accordance with official recommendations."

Attachment 1. Product Information

NAME OF THE MEDICINE

Menveo® powder and solvent for solution for injection
Meningococcal (Groups A, C, W-135 and Y) Oligosaccharide CRM_{197} Conjugate Vaccine
Pharmacotherapeutic group: Meningococcal vaccines, ATC code: JO7AH08.

DESCRIPTION

Menveo consists of one vial containing the lyophilised MenA Conjugate Component plus excipients, and one syringe containing the liquid MenCWY Conjugate Component plus excipients. The reconstituted sterile liquid vaccine is administered by intramuscular injection and contains meningococcal serogroup A, C, W-135 and Y oligosaccharides conjugated individually to *Corynebacterium diphtheriae* CRM_{197} protein. The polysaccharides are produced from fermentation and purification of *Neisseria meningitidis* (serogroups A, C, W-135 or Y). MenA, MenW-135 and MenY polysaccharides are purified by several extraction and precipitation steps. MenC polysaccharide is purified by a combination of chromatography and precipitation steps. The protein carrier (CRM_{197}) is produced by bacterial fermentation and is purified by a series of chromatography and ultrafiltration steps.

The oligosaccharides are prepared by hydrolysis, sizing, activation and conjugation. Each oligosaccharide is covalently linked to the CRM_{197}. The resulting glycoconjugates are purified to yield the four drug substances, which compose the final vaccine. No preservative or adjuvant is added during manufacturing. The vaccine contains no thiomersal.

Menveo is presented as a vial (type I glass) of MenA lyophilized Conjugate Component with a synthetic rubber stopper + syringe (type I glass) of MenCWY liquid Conjugate Component and a tip cap (type I elastomeric closure with 10 % Dry Natural Rubber: latex).

PHARMACOLOGY

Mechanism of Action
Meningococcal disease is caused by a gram-negative diplococcus, *Neisseria meningitidis*. *N. meningitidis* causes life-threatening disease worldwide. Based on antigenic variations in capsular polysaccharide structure, 13 serogroups of *N. meningitidis* have been identified.

Globally, 5 serogroups, A, B, C, W-135 and Y, cause almost all invasive meningococcal infections. Invasive infection by *N. meningitidis* most often manifests as bacteremia and/or meningitis and can also more rarely present as arthritis, myocarditis, pericarditis, endophthalmitis, pneumonia or infection at other anatomic sites.

Early clinical manifestations of meningococcal disease are often nonspecific and may initially be difficult to distinguish from less serious illnesses. Symptoms may include

headache, stiff neck, fever, chills, malaise and prostration. Disease can progress rapidly, with most cases seeking medical attention within 24 hours of symptom onset. About 10% of cases die, even with appropriate antimicrobial and supportive treatment; with meningococcal septicemia up to 40% of cases die (Rosenstein, 1999). Permanent sequelae, including scarring, limb or digit loss, neurologic dysfunction, and/or hearing loss occur in 11–19% of survivors (Erickson, 1998).

Asymptomatic colonization of the upper respiratory tract by encapsulated *N. meningitidis* is common. Transmission is thought to occur by droplet transmission of respiratory tract secretions. Only a small percentage of colonized individuals develop disease.
The incidence of meningococcal disease is highest in children under 5 years old, with infants under 12 months old at the greatest risk. Another incidence peak occurs in adolescents.

Bactericidal anti-capsular antibodies protect against invasive meningococcal disease. Vaccination with Menveo leads to the production of bactericidal antibodies directed against the capsular polysaccharides of serogroups A, C, W-135 and Y. The original correlate of protection against meningococcal disease was a bactericidal activity (using human serum as the complement source (hSBA)) titer of ≥1:4 (Goldschneider, J. Exp Med, 1969); an hSBA titer ≥1:8 is a more conservative correlate of protection.

CLINICAL TRIALS
The immunogenicity of Menveo was assessed in five clinical trials. The number of subjects who provided immunogenicity data (a subset of the full populations) was 6185. The primary serologic endpoint for many of the clinical trials was seroresponse. This was defined as a post vaccination titer of ≥1:8 for subjects who were seronegative at baseline, or a four fold rise for subjects who were seropositive at baseline. Other endpoints included the proportion of subjects who had post vaccination titers of ≥1:8 or ≥1:4 and geometric mean titers (GMTs).

Correlate of Protection Due to the infrequency of clinical disease, the efficacy of Menveo is inferred from the results of a functional assay. The primary measure of immune response and protection was induction of serogroup-specific anti-capsular antibodies with bactericidal activity. Serum bactericidal activity (SBA) was measured using human serum as the source of exogenous complement (hSBA). The hSBA was the original correlate of protection against meningococcal disease (Goldschneider I., et al, 1969 a, b).

Demonstration of immunologic non-inferiority to Menactra® (Sanofi Pasteur) among subjects aged 11-55 years. Immunogenicity was evaluated in a Phase 3, randomized, multicenter, active controlled clinical trial V59P13 that enrolled adolescents (11-18 years of age) and adults (19-55 years of age). Participants received either a dose of Menveo (N = 2649) or Menactra (N = 875). Sera were obtained both before vaccination and 28 days after vaccination. Demographic characteristics between Menveo and Menactra vaccine groups were comparable within each age group.

Immunogenicity in Adolescents

In the 11 to 18 year old population of the pivotal study, V59P13, noninferiority of Menveo to Menactra was demonstrated for all four serogroups using the primary endpoint (hSBA seroresponse) and two secondary endpoints, percentage of all subjects with 1-month post-vaccination hSBA titer ≥ 1:8, and geometric mean titer (GMT). Furthermore, hSBA GMTs for all four serogroups were statistically superior in the Menveo group, as compared to the Menactra group. The percentages of subjects with hSBA seroresponse and with hSBA titer ≥ 1:8 were statistically superior for serogroups A, W, and Y in the Menveo group, as compared to the Menactra group (Table 1). The clinical relevance of higher immune responses is uncertain.

Table 1: Comparison of bactericidal antibody responses† to Menveo and Menactra 28 days after vaccination of subjects aged 11-18 years

	Bactericidal Antibody Response†		Comparison of Menveo and Menactra	
Endpoint by Serogroup	**Menveo (95% CI)**	**Menactra (95% CI)**	**Menveo / Menactra (95% CI)**	**Menveo minus Menactra (95% CI)**
A	N=1075	N=359		
% Seroresponse‡	75 (72, 77)	66 (61, 71)		8 (3, 14)* §
% ≥ 1:8	75 (73 , 78)	67 (62, 72)	-	8 (3, 14)
GMT	29 (24 , 35)	18 (14, 23)	1.63 (1.31, 2.02)	-
C	N=1483	N=501		
% Seroresponse‡	75 (73, 77)	73 (69, 77)		2 (-2, 7)*
% ≥ 1:8	84 (82, 86)	84 (80, 87)	-	1 (-3, 5)
GMT	59 (48, 73)	47 (36, 61)	1.27 (1.01, 1.6)	-
W-135	N=1024	N=288		
% Seroresponse‡	75 (72, 77)	63 (57, 68)		12 (6, 18)*§
% ≥ 1:8	96 (95, 97)	88 (84, 92)	-	8 (4, 12)
GMT	87 (74, 102)	44 (35, 54)	2.00 (1.66, 2.42)	-
Y	N=1036	N=294		
% Seroresponse‡	68 (65, 71)	41 (35, 47)		27 (20, 33)* §
% ≥ 1:8	88 (85, 90)	69 (63, 74)	-	19 (14, 25)
GMT	51 (42, 61)	18 (14, 23)	2.82 (2.26, 3.52)	-

† Serum Bactericidal Assay with exogenous human complement source (hSBA). ‡ Seronegative was defined as a pre-vaccination hSBA titer of <1:4. Among the seronegative subjects, the seroresponse endpoint was defined as a post vaccination titer of > 1:8.

* noninferiority criterion met (the lower limit of the two-sided 95% CI >-10 % for vaccine group differences (Menveo minus Menactra), >0.5 for vaccine group ratios (Menveo/Menactra)

§ superiority criterion met (the lower limit of two-sided 95% CI >0% for vaccine group differences).

In the non-inferiority study, V59P6, immunogenicity was assessed among adolescents aged 11-17 years who had been randomized to receive either Menveo or Menomune® (Sanofi Pasteur Ltd), a quadrivalent meningococcal polysaccharide vaccine. Responses to Menveo were shown to be non-inferior to those to Menomune for all four serogroups (A, C, W and Y) based on seroresponse, proportions achieving hSBA titres ≥ 1:8, and GMTs. At one year post vaccination, the percentage of Menveo recipients with hSBA titers ≥ 1:8

remained significantly higher compared with Menomune recipients for serogroups C, W and Y, and similar between the two study groups for serogroup A (Table 2).

Table 2: Comparison of bactericidal antibody responses† to Menveo and Menomune 28 days after vaccination of subjects aged 11-17 years

	Seroresponse			hSBA Titer≥ 1:8			hSBA GMTs		
	Menveo	**Menomune**	**Vaccine differences ‡**	**Menveo**	**Menomune**	**Menveo minus Menomune**	**Menveo**	**Menomune**	**Menveo / Menomune †**
A	N=148	N=179		N=148	N=179		N=148	N=179	
	80% (73, 86)	41% (34, 49)	39% (29, 48)**	81% (74, 87)	41% (34, 49)	40% (30, 49)*	34 (26, 44)	6.97 (5.51, 8.82)	4.87 (3.41, 6.95)*
C	N=148	N=177		N=148	N=177		N=148	N=177	
	76% (68, 82)	54% (47, 62)	21% (11, 31)**	83% (76, 89)	63% (56, 70)	20% (10, 29)*	58 (39, 85)	30 (21, 43)	1.9 (1.13, 3,19)*
W	N=146	N=173		N=146	N=173		N=146	N=173	
	84% (77, 90)	71% (63, 77)	14% (5, 23)**	90% (84, 95)	86% (80, 91)	4% (-3, 11)*	49 (39, 62)	30 (24, 37)	1.65 (1.22, 2.24)*
Y	N=147	N=177		N=147	N=177		N=147	N=177	
	86% (79, 91)	66% (59, 73)	20% (11, 28)**	95% (90, 98)	81% (74, 86)	14% (7, 21)*	100 (74, 134)	34 (26, 45)	2.91 (1.99, 4.27)*

‡Difference in proportions for MenACWY minus Menomune.

† Ratio of GMTs for MenACWY to Menomune.

* noninferiority criterion met (the lower limit of the two-sided 95% CI >-10 % for vaccine group differences (Menveo minus Menomune), >0.5 for vaccine group ratios (Menveo/Menomune)

** the seroresponse was statistically higher (the lower limit of the two-sided 95% CI >0% for vaccine group differences).

Immunogenicity in Adults

In the 19 to 55 year population of the pivotal study, V59P13, noninferiority of responses to Menveo to those to Menactra was demonstrated for all four serogroups using all three endpoints (seroresponse [primary endpoint], hSBA titer ≥ 1:8, and hSBA GMTs). Furthermore, both hSBA GMTs and the percentage of subjects with hSBA seroresponse were statistically superior for serogroups C, W, and Y in the Menveo group, as compared to the Menactra group. The percentage of subjects with hSBA titer ≥ 1:8 was statistically superior for serogroups C and Y in the Menveo group, as compared to the Menactra group (Table 3). The clinical relevance of higher immune responses is uncertain.

Table 3: Comparison of bactericidal antibody responses† to Menveo and Menactra 28 days after vaccination of subjects aged 19-55 years

	Bactericidal Antibody Response†		Comparison of Menveo and Menactra	
Endpoint by Serogroup	**Menveo (95% CI)**	**Menactra (95% CI)**	**Menveo / Menactra (95% CI)**	**Menveo minus Menactra (95% CI)**
A	N=963	N=321		
% Seroresponse‡	67 (64, 70)	68 (63, 73)		-1 (-7, 5)*
% ≥ 1:8	69 (66, 72)	71 (65, 76)	-	-2 (-7, 4)
GMT	31 (27, 36)	30 (24, 37)	1.06 (0.82, 1.37)	-
C	N=961	N=318		
% Seroresponse‡	67 (64, 70)	58 (53, 64)		9 (3, 15)* §
% ≥ 1:8	80 (77, 83)	72 (67, 77)	-	8 (3, 14)
GMT	52 (44, 60)	32 (25, 40)	1.63 (1.24, 2.13)	-
W-135	N=484	N=292		
% Seroresponse‡	50 (46, 55)	41 (35, 47)		9 (2, 17)* §
% ≥ 1:8	94 (91, 96)	90 (86, 93)	-	4 (0, 9)
GMT	111 (93, 132)	69 (55, 85)	1.61 (1.24, 2.1)	-
Y	N=503	N=306		
% Seroresponse‡	56 (51, 60)	40 (34, 46)		16 (9, 23)* §
% ≥ 1:8	79 (76, 83)	70 (65, 75)	-	9 (3, 15)
GMT	44 (37, 52)	21 (17, 26)	2.10 (1.60, 2.75)	-

† Serum Bactericidal Assay with exogenous human complement source (hSBA).

‡ Seronegative was defined as a pre-vaccination hSBA titer of <1:4. Among the seronegative subjects, the seroresponse endpoint was defined as a post vaccination titer of > 1:8.

*noninferiority criterion met (the lower limit of the two-sided 95% CI >-10 % for vaccine group differences (Menveo minus Menomune), >0.5 for vaccine group ratios (Menveo/Menomune))

§ superiority criterion met (the lower limit of two-sided 95% CI >0% for vaccine group difference).

INDICATIONS

Menveo is indicated for active immunization of adolescents (from 11 years of age) and adults to prevent invasive disease caused by *Neisseria meningitidis* serogroups A, C, W135 and Y. The use of this vaccine should be in accordance with official recommendations.

CONTRAINDICATIONS

- Known hypersensitivity to any component of Menveo vaccine, including CRM_{197}
- Known hypersensitivity to other diphtheria-containing vaccines;
- Known hypersensitivity to latex. The tip cap of the syringe contains 10% Dry Natural Rubber. Dry Natural Rubber is considered to present a much lower risk of allergy compared with natural rubber latex. Notwithstanding this, the healthcare professional is encouraged to consider the benefit: risk prior to administering this vaccine to patients with known history of hypersensitivity to latex.
- Acute febrile illness of any cause;
- A life-threatening reaction after previous administration of a vaccine containing similar components is a contraindication to vaccine administration.

PRECAUTIONS

Menveo has not been evaluated in persons with thrombocytopenia or bleeding disorders. Because of the risk of hematoma, Menveo should not be administered to persons with any bleeding disorder, such as hemophilia or thrombocytopenia, or to persons receiving anticoagulant therapy, unless the potential benefit outweighs the risk of administration. When intramuscular vaccine is indicated for a patient with a bleeding disorder or a person receiving anticoagulant therapy, the vaccine should be administered intramuscularly if, in the opinion of a physician familiar with the patient's bleeding risk, the vaccine can be administered with reasonable safety by this route. If the patient receives antihemophilia or similar therapy, intramuscular vaccinations can be scheduled shortly after such therapy is administered. A fine needle (23 gauge or finer) should be used for the vaccination and firm pressure applied to the site, without rubbing, for 2 minutes or more. The patient or family should be instructed concerning the risk of hematoma from the injection.

Appropriate precautions should be taken before administration of Menveo to minimize the risk of adverse reactions. These precautions include reviewing the subject's

immunization and medical history for the presence of any contraindications to immunization, such as possible hypersensitivity to Menveo or similar vaccines (including diphtheria-containing vaccines), and evaluating the patient's current health status.

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

As for all vaccines, the date of vaccine administration, the lot number and the manufacturer of the vaccine administered should be recorded in the patient's immunization record.

Care should be taken to avoid injecting Menveo vaccine subcutaneously, since clinical studies have not been conducted to establish the vaccine's safety and immunogenicity when administered subcutaneously.

A separate sterile syringe and needle should be used for each patient to prevent transmission of blood-borne infectious agents from person to person. Needles should not be recapped and should be disposed of according to guidelines for management of biohazardous waste.

Menveo is not indicated to prevent invasive meningococcal disease caused by serogroup B *N. meningitidis* nor to prevent infections caused by other microorganisms.

Menveo is not indicated for treatment of meningococcal disease.

The immune response to Menveo vaccine administered to immunosuppressed persons has not been studied.

A possible association between Guillain-Barré Syndrome (GBS) and receipt of the US and Canadian licensed quadrivalent diphtheria toxoid conjugate A, C, W-135 and Y vaccine (Menactra®, sanofi Pasteur) was reported in 2005. At present, it is unclear if this represents a true or a fortuitous association. The US Centers for Disease Control and Prevention (CDC) conducted an analysis of the 17 cases of GBS occurring among Menactra recipients and concluded that the relative risk for GBS post Menactra, relative to the background risk in the general population, was 1.78 (95% CI 1.02-2.85). Since the background rate of GBS is very low (0.1/100,000 person months) and the disease is generally self-limited with a low case fatality rate in this population, this equates to an extremely small burden of attributable disease impact. In subsequent analysis, when factoring in the prevention of meningococcal disease, and thus the overall risk/benefit balance, the CDC concluded that vaccination was clearly beneficial, with vaccination saving 2400 Quality Adjusted Life Years (QALYs) due to prevention of meningococcal disease, at a cost of 5 QALYs due to vaccine induced GBS (Cho, 2010). On this basis, vaccination was judged to be the preferred strategy and for this reason, the recommendation for routine use of Menactra in adolescents continues.

Paediatric Populations

Safety and immunogenicity of Menveo in children under 11 years old have not been established.

Fertility

There were no effects on maintaining performance or fertility of female rabbits receiving the clinical dose of Menveo three times pre-mating and twice during gestation. Each dose was approximately 15-fold higher than the human dose on body weight basis. Impairment of male fertility in rabbits was not evaluated.

Use in Pregnancy (Category B1)

Insufficient clinical data on exposed pregnancies are available.

No information is available on administration of Menveo to pregnant women. Menveo vaccine should be given to pregnant women following assessment of the risk and benefit.

In a study in rabbits immunised with Menveo three times prior to mating, and on gestation days 7 and 20, there were no treatment-related effects on pregnancy, fetuses, or kits. Antibodies to the vaccine were detected in vaccine-treated dams, fetuses, and kits.

Use in Lactation

It is not known whether Menveo is extracted in human milk. However, as with other polysaccharide vaccines , it is not expected for vaccination with Menveo to harm the mother or the infant. Menveo should only be administered to women who are breastfeeding when needed and the possible advantages outweigh the possible risks.

Menveo administration to maternal animals prior to mating and during gestation had no effects on development of offspring, assessed to lactation day 29. The vaccine was immunogenic in maternal animals and antibodies were detected in the offspring, but antibodies levels in milk were not determined.

Carcinogenesis, Mutagenesis

Carcinogenesis and mutagenesis studies have not been performed with Menveo.

Interaction with other medicines

Menveo must not be mixed with other vaccines in the same syringe. Separate injection sites must be used if more than one vaccine is being administered.

Menveo has been evaluated in a concomitant vaccination study with Tetanus, Reduced Diphtheria and Acellular Pertussis Vaccine, Adsorbed (Boostrix®; GlaxoSmithKline

Biologicals (Tdap)) + Human Papillomavirus Quadrivalent (Types 6, 11, 16 and 18) Vaccine, Recombinant (GARDASIL®, Merck and Co., Inc.).

The immune response to Menveo when given concomitantly with or sequentially after Tdap (Tdap at day 1 followed by Menveo at month 1) (Table 4) was non-inferior to the immune response when Menveo vaccine was given alone at day 1. The immune response to Tdap when given concomitantly with Menveo was non-inferior to the immune response when Tdap was given alone at day 1 for Diphtheria and Tetanus antigens. For pertussis antigens it was non-inferior for pertussis toxin (PT) antigen only, with statistically inferior responses to filamentous hemagglutinin (FHA) and pertactin. The reductions in FHA and pertactin responses are not thought to be clinically significant.

Table 4: Comparison of antibody responses* to Menveo and Tdap vaccines for subjects 11 to 18 years of age 1 month following vaccination

			Menveo + Tdap		**Menveo → Tdap**		**Tdap→ Menveo**
Antigen	Endpoint	N	Mean or % (95% CI)	N	Mean or % (95% CI)	N	Mean or % (95% CI)
Tetanus	% ≥1.0 IU/mL (95% CI)	495	100% (99, 100)	459	100% (99, 100)	487	100% (99, 100)
Diphtheria	% ≥1.0 IU/mL (95% CI)	495	100% (99, 100)	459	100% (99, 100)	487	98% (96, 99)
Anti – PT	GMC (95% CI)	482	51 (47, 55)	452	79 (73, 87)	477	63 (58, 69)
Anti – FHA	GMC (95% CI)	492	341 (310, 375)	458	1107 (989, 1238)	485	511 (464, 563)
Anti – Pertactin	GMC (95% CI)	495	824 (732, 928)	459	1563 (1390, 1758)	487	1198 (1063, 1351)
Serogroup*		N		N		N	
A	% ≥ 1:8 (95% CI)	497	81% (78, 85)	486	82% (79, 86)	458	89% (85, 91)
	GMT (95% CI)	497	62 (52, 74)	486	67 (56, 80)	458	95 (79, 113)
C	% ≥ 1:8 (95% CI)	497	92% (89, 94)	487	90% (87, 93)	457	93% (90, 95)
	GMT (95% CI)	497	66 (56, 77)	487	70 (60, 83)	457	68 (58, 79)
W-135	% ≥ 1:8 (95% CI)	490	98% (96, 99)	474	99% (98, 100)	458	95% (93, 97)
	GMT (95% CI)	490	146 (129, 165)	474	159 (140, 181)	458	104 (91, 119)
Y	% ≥ 1:8 (95% CI)	496	93% (90, 95)	497	93% (90, 95)	460	92% (90, 95)
	GMT (95% CI)	496	72 (62, 84)	487	81 (70, 95)	460	57 (49, 67)

** For Menveo, Serum Bactericidal Assay with exogenous human complement source (hSBA).*

ADVERSE EFFECTS

The safety of Menveo was evaluated in 5 randomized controlled clinical trials including 6724 participants (from 11 years of age through adulthood) who received Menveo and 1966 who received a comparator vaccine (either Menomune or Menactra). Demographic characteristics of subjects who received Menveo were similar to those who received the comparator vaccine.

Among Menveo recipients, 61%, 17% and 22% were in the 11-18 year, 19-34 year and 35-55 year age groups, respectively. Among Menactra recipients, 31%, 32% and 37% were in the 11-18 year, 19-34 year and 35-55 year age groups, respectively, and among Menomune recipients, 100% were in the 11-18 year age group.

The two primary safety studies were randomized, active-controlled trials that enrolled participants aged 11 to 55 years (Menveo, N=2663; Menactra N=876) and 19 to 55 years (Menveo, N=1606; Menactra, N=899), respectively.

Undesirable effects reported in three pivotal and 2 supportive clinical trials are listed here below per system organ class. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Frequencies are defined as follows:

Very common: (≥ 1/10)
Common: (≥1/100 to <1/10)
Uncommon: (≥1/1,000 to <1/100)
Rare: (≥1/10,000 to <1/1,000)
Very rare: (<1/10,000)

Infections and infestations:
Uncommon: nasopharyngitis

Nervous system disorders:
Very common: headache
Uncommon: dizziness

Gastrointestinal disorders:
Very common: nausea

Skin and subcutaneous tissue disorders:
Common: rash

General disorders and administration site conditions:
Very common: injection site pain, injection site erythema (≤ 50 mm), injection site induration (≤ 50 mm), malaise
Common: injection site erythema (> 50 mm), injection site induration (> 50 mm), fever ≥ 38°C, chills

DOSAGE AND ADMINISTRATION

Menveo should be administered as a single 0.5 mL injection. The need for, and timing of, a booster dose of Menveo has not yet been determined.

Preparation for Administration

Menveo must be prepared for administration by reconstituting the lyophilized MenA conjugate component with the liquid MenCWY conjugate component.

Remove the tip cap from the syringe and attach a suitable needle for the withdrawal (21G 1 1/2). Use the whole contents of the syringe to reconstitute the MenA conjugate component vial.

Gently shake the vial until the lyophilised vaccine plug has dissolved. Withdraw the full contents of the vial into the syringe. Please note that it is normal for a small amount of liquid to remain in the vial following withdrawal of the dose. Prior to injection, change the needle with one suitable for the administration (25G 1). Ensure that no air bubbles are present in the syringe before injecting the vaccine.

Following reconstitution, the vaccine is a clear, colourless solution, free from visible foreign particles. In the event of any foreign particulate matter and/or variation of physical aspect being observed, discard the vaccine.

Method of administration

Menveo should be administered as a single 0.5mL intramuscular injection, preferably into the deltoid muscle. Do not administer Menveo intravenously, subcutaneously or intradermally.

Menveo must not be mixed with other vaccines in the same syringe. Separate injection sites must be used if more than one vaccine is being administered at the same time.

Menveo is for single use in one patient only.

OVERDOSAGE

No case of overdose has been reported.

In case of overdose, immediately contact the Poisons Information Centre on 13 11 26 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

Menveo is presented in a type I glass vial containing the MenA lyophilised conjugate component with a halobutyl rubber stopper and a type I glass syringe containing the - MenCWY liquid conjugate component. The syringe has a tip cap (type I elastomeric closure with 10% of Dry Natural rubber). Each pack contains a single dose.

One dose (0.5 ml of the reconstituted vaccine) contains:

Meningococcal oligosaccharide – group A*	10 micrograms
Conjugated to *Corynebacterium diphtheriae* CRM_{197} protein	16.7 to 33.3 micrograms
Meningococcal oligosaccharide - group C*	5 micrograms
Conjugated to *Corynebacterium diphtheriae* CRM_{197} protein	7.1 to 12.5 micrograms
Meningococcal oligosaccharide - group W-135*	5 micrograms
Conjugated to *Corynebacterium diphtheriae* CRM_{197} protein	3.3 to 8.3 micrograms
Meningococcal oligosaccharide - group Y*	5 micrograms
Conjugated to *Corynebacterium diphtheriae* CRM_{197} protein	5.6 to 10 micrograms

*Prepared from *Neisseria meningitidis*

List of excipients

Vial containing MenA lyophilised conjugate component

- Sucrose

- Potassium dihydrogen phosphate

Syringe containing MenCWY liquid conjugate component

- Sodium phosphate monobasic monohydrate

- Sodium phosphate dibasic dihydrate

- Sodium chloride

- Water for Injections

Shelf life and Storage Conditions

3 years (unreconstituted).

Store between 2° and 8°C away from a freezer compartment. DO NOT FREEZE. Product that has been frozen should not be used. Keep the vial and the syringe in the outer carton in order to protect from light. Do not use after the expiry date.

Following reconstitution, to reduce microbiological hazard the product should be used as soon as practicable after reconstitution. If storage is necessary, hold at 2-8 °C for not more than 24 hours. The two components of the product may have different expiry dates. The outer carton bears the earlier of the two dates and the product should be used before this date. The carton and ALL of its contents must be discarded on reaching this outer carton expiry date.

NAME AND ADDRESS OF THE SPONSOR

Novartis Vaccines & Diagnostics Pty Ltd
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North Ryde, NSW 2113

POISON SCHEDULE OF THE MEDICINE

Schedule 4 (Prescription-Only Medicine)

MENVEO meningococcal (Groups A, C, W-135 and Y) oligosaccharide CRM_{197} conjugate vaccine (AUST R 158477)

DATE OF APPROVAL

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Version 2

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