



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Meningococcal (Groups A, C, W- 135 and Y) oligosaccharide CRM197 conjugate vaccine

Proprietary Product Name: Menveo

Sponsor: GlaxoSmithKline Australia Pty Ltd

April 2018

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- 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; it provides information that relates to a submission at a particular point in time.
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Common abbreviations

Abbreviation	Meaning
AE	Adverse event
CBER	Center for Biologics Evaluation and Research
CQA	Clinical Quality Assurance Group (within Novartis)
CR	Complete Response
CRA	Clinical research associate
CRF	Case report form
eCRF	Electronic case report form
CRO	Clinical Research Organization
CSR	Clinical study report
EDC	electronic data capture
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
LA/ LATAM	Latin America
MAAEs	unsolicited AE that results in a visit to a medical office or emergency room visit
MCAR	missing completely at random
MenACWY	Meningococcal (Group A, C, Y and W135)
MMC	Menveo metadata collection project
MMRV	Measles, mumps, rubella, and varicella
NCR	non-carbon copy
PP	Primary per protocol
RSS	Restricted Safety Set
RPS	Research Pharmaceutical Services, Inc.
SAE	Serious adverse event

Abbreviation	Meaning
sBLA	supplemental Biologics License Application
SOP	Standard Operational Procedure
TMF	Trial master file
US	United States

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	Extension of indications
<i>Decision:</i>	Approved
<i>Date of decision:</i>	3 July 2017
<i>Date of entry onto ARTG</i>	5 July 2017
<i>Active ingredient(s):</i>	Meningococcal (Groups A,C,W-135 and Y) oligosaccharide CRM197 conjugate vaccine
<i>Product name(s):</i>	Menveo
<i>Sponsor's name and address:</i>	GlaxoSmithKline Australia Pty Ltd PO Box 18095 Melbourne VIC 8003
<i>Dose form(s):</i>	Injection, solution and Injection, powder
<i>Strength(s):</i>	Solution: Diphtheria CRM197 protein 16 µg/Meningococcal oligosaccharide group C 5 µg /Meningococcal oligosaccharide group W135 5 µg /Meningococcal oligosaccharide group Y 5 µg Powder: Diphtheria CRM197 protein 16.7 µg and Meningococcal oligosaccharide group A 10 µg
<i>Container(s):</i>	Menveo is presented in a Type I glass vial containing the MenA lyophilised conjugate component with a halobutyl rubber stopper. The MenCWY liquid conjugate component is presented either in a Type I glass syringe or a Type I glass vial. The syringe has a tip cap (Type I elastomeric closure with 10% of Dry Natural rubber). The vial has a butyl rubber stopper.
<i>Pack size(s):</i>	The vial/syringe presentation is presented in single-dose packs. The vial/vial presentation is presented in single-dose (2 vials) and 5-doses (10 vials) multi-packs. Not all presentations and pack sizes may be marketed.
<i>Approved therapeutic use:</i>	<i>Menveo is indicated for active immunisation of infants and children (from 2 months of age), adolescents 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.</i>
<i>Route(s) of administration:</i>	Intramuscular (IM)
<i>Dosage:</i>	<i>Vaccine schedule for children from 2 to 23 months of age</i>

Infants initiating vaccination from 2 to 6 months of age

First three doses of Menveo, each of 0.5 mL, should be given with an interval of at least 2 months; the fourth dose should be administered during the second year of life (at 12-16 months).

Unvaccinated children from 7 to 23 months of age

Menveo should be administered as two doses, each as a single dose (0.5 mL), with the second dose administered in the second year of life and at least two months after the first dose.

Vaccine schedule for children 2 to 10 years of age

Menveo should be administered as a single 0.5 mL injection.

ARTG number (s): AUST R 158447 (vial syringe) and AUST R 192696 (vial/vial)

Product background

Menveo is currently registered to immunize individuals 11 years of age and over to prevent invasive disease caused by *Neisseria meningitidis* serogroups A, C, W135 and Y.

This AusPAR describes the application by the sponsor to extend the indication for Menveo to include immunisation of infants over 2 months of age and children.

This application was submitted in consultation with the Office of Health Protection in the Commonwealth Department of Health due to the public health environment surrounding meningococcal disease. The submitted dossier was consistent with the data package submitted in the US for the same indication.

Menveo is supplied as one vial containing lyophilised MenA conjugate component and one syringe or vial containing liquid MenCWY conjugate component. The reconstituted vaccine is for single intramuscular injection (0.5 mL) containing meningococcal serogroup A (10 µg), C (5µg), W-135 (5 µg) and Y (5 µg) oligosaccharides individually conjugated with *Corynebacterium diphtheriae* (CRM197) protein carrier. This vaccine product does not contain any preservative or adjuvant and is thiomersal free.

The approved dose is one 0.5mL intramuscular (IM) injection. The proposed vaccination schedule is dependent on age and prior vaccination with Menveo: The extension to the younger age group proposes a 4 dose schedule in infants (at 2, 4, 6, 12 to 16 months of age). The fourth dose should be administered during the second year of life (at 12-16 months) This extension application also proposes a 2 dose catch-up schedule in unvaccinated infants between 7th and 23rd month with the with the second dose administered in the second year of life and at least two months after the first dose. A single dose schedule is proposed in the 2 to 10 years age group (same as current approval in adolescents and adults).

At present in Australia, no tetravalent conjugate meningococcal vaccine (MenACWY) is approved for use in infants less than 12 months of age (Menactra from 2-55 years age; Nimenrix from 1-55 years age). The approved monovalent C conjugate vaccines (Neisvac-C; Meningitec; Menjugate) can be used from 6 weeks of age. MenC is also available combined with Hib (Menitorix) from 6 weeks of age. A multi-component meningococcal B vaccine (Bexsero) is approved in infants from 2 months of age. Two polysaccharide tetravalent (ACWY-PC) vaccines (Menomune and Mencevax from 2 years of age and above) are also registered.

The most at-risk groups in community are age groups <5 years, 15-24 years and elderly. The infection is rare (incidence 3.5/100,000 in 2002 in Australia) but serious which can be

rapidly fatal. The incidence has been declining with the introduction of MenC vaccine (1.1/100,000 cases in 2016). The most common infection over the past decade was serotype B (0.4/100,000 cases in 2016). However, serotype W infection has been on the rise since 2013 with 110 reported cases in 2016 compared to 92 cases of serotype B. As a result, State based ACWY vaccination is being introduced in School Years 11 and 12 with the 2017 winter season.¹

Menveo is approved in the USA from 2 months of age, whereas the approval in EU is from 2 years of age. Approval in the US was granted in 2013 for a 4 dose series in infants 2 months and over, 2 dose catch-up in infants 7 to 23 months and a single dose in children 2-10 years of age, as is being proposed here.

Information on the condition being treated

Meningococcal disease is caused by a gram-negative diplococcus, *Neisseria meningitidis*. *N. meningitidis* is a gram negative diplococcus which causes life-threatening disease worldwide. It has no natural animal reservoir and survives in human oropharynx of carriers. 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 bacteraemia and/or meningitis and can also more rarely present as arthritis, myocarditis, pericarditis, endophthalmitis, pneumonia or infection at other anatomic sites. Symptoms of infection may include headache, stiff neck, fever, chills, malaise and prostration. Disease can progress rapidly. About 10% of cases die, even with appropriate antimicrobial and supportive treatment; with meningococcal septicaemia up to 40% of cases die. The most common meningococcal diseases in Australia are caused by serogroups W followed by B and Y with few cases caused by serogroups A. Children under 5 years of age and young adults aged 15 to 24 years are at the highest risk of acquiring meningococcal disease.

Current treatment options

There are antibiotics to treat meningococcal infection. Even with appropriate antibiotic treatment, meningococcal infection has a significant mortality and a high morbidity. MenACWY vaccine provides broad serogroup coverage (that is, for serogroups A, C, W, and Y) for vaccination against Meningococcal infection.

MenACWY is currently registered to immunise individuals 11 years of age and over to prevent invasive disease caused by *Neisseria meningitidis* serogroups A, C, W135 and Y. This application proposes to extend the indication to include immunisation of infants over 2 months of age and children.

The application was submitted, following discussions between the Department of Health, TGA and GSK Australia.

Regulatory status

Australian regulatory history

MenACWY was approved for use in adolescents and adults 11-55 years of age in May 2010. MenACWY is currently indicated for active immunisation of adolescents (from 11 years of age) and adults to prevent invasive disease caused by *Neisseria meningitidis*

¹ NCIRS Fact Sheet

serogroups A, C, W135 and Y. The use of this vaccine should be in accordance with official recommendations.

Overseas regulatory history

MenACWY is approved in the US and Canada for immunisation of infants (>2 months of age), children, adolescents and adults. MenACWY was approved for immunisation of infants over 2 months of age and children in the USA in August 2013 and in Canada in December 2014.

MenACWY was also approved in Europe via a centralised procedure to the European Medicines Agency (EMA) for use in children 2 to 10 years of age in March 2012.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

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 CRM197 carrier protein is extracted and purified from a non-toxicogenic 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 is no viral safety or transmissible spongiform encephalopathies (TSE) issues. In addition, the use of material derived from human or animal sources has been kept to a minimum.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

There are antibiotics to treat meningococcal infection. Even with appropriate antibiotic treatment, meningococcal infection has a significant mortality and a high morbidity.

MenACWY vaccine provides broad serogroup coverage (that is, for serogroups A, C, W, and Y) for vaccination against Meningococcal infection.

MenACWY is currently registered to immunize individuals 11 years of age and over to prevent invasive disease caused by *Neisseria meningitidis* serogroups A, C, W135 and Y. This application proposes to extend the indication to include immunisation of infants over 2 months of age and children. The application is being submitted, following discussions between the Department of Health, TGA and GSK Australia.

Guidance

In contrast to the application for use in 11 to 55 year olds which used single dose vaccination regimen, the current submission involves multidose regimens, mainly 4 dose primary vaccination in infant/toddlers. The results observed after the first of a 2 dose infant/toddler series in studies V59P7 and V59P9 indicated that an additional dose would provide a substantial increase in the proportion of subjects achieving hSBA $\geq 1:8$ and in the short-term persistence of bactericidal antibodies.

Based on these considerations and a Phase II study specifically examining immunogenicity in infants (V59P5) it was decided that the proposed primary regimen for young infants would be a 4 dose schedule at 2, 4, and 6 months of age, with a fourth dose to be administered in the second year of life, and that the proposed catch-up dosing regimen for immunologically naïve older infants ≥ 6 months of age would be 2 doses, separated by at least 2 months, with the second dose given in the second year of life.

There is no change in formulation.

Contents of the clinical dossier

- 3 dose-finding/supportive studies.
- 5 pivotal efficacy/safety studies.
- 1 other efficacy/safety studies.

The dossier documented a development program of dose-finding, pivotal and other clinical trials relating to the proposed extension of indications.

Clinical data is provided to support 2 specific age groups:

- Infants/toddlers: 2 months to 23 months of age
- Children: 2 to 10 years of age

Infants/toddlers:

The pivotal immunogenicity and safety studies supporting this age group are:

- a. V59P14 and V59_33 supporting a 4 dose series infant schedule,
- b. V59P21 supporting a 2 dose series in children over 6 months of age who did not receive a 4 dose schedule,
- c. Pivotal safety Study V59P23 in children receiving a 4 dose series concomitantly with routine infant toddler vaccines.

Children

V59P20: safety and efficacy study for 1 or 2 dose regimens in children 2 to 10 years.

Paediatric data

All the studies included in this submission are paediatric.

Good clinical practice (GCP)

During the original review of the data collected in the US, the TGA had some concerns with the conduct of Studies V59P14, V59P21, and US sites in V59P23. These related mainly to the manner of collection some of the safety data that allowed for reconstruction, as there were no time frames set for the recollection and documentation of the data (collected in diaries). Following this, there was an extensive effort by the applicant to verify the reliability of the safety data. They also identified a site at which GCP had not been applied (and so this site was excluded from all analysis). Also, initially immunogenicity evaluations were not blinded for Study V59P14. After discussions, remaining serum samples were re-tested in a blinded manner and the applicant found concordance with the previous assay results.

Pharmacokinetics

No new studies submitted.

Pharmacodynamics

For vaccination studies, pharmacodynamics is generally measured in terms of immunogenicity.

Dosage selection for the pivotal studies

Dosage per vaccination is unchanged. Previous submissions of this vaccine for individuals 11 to 55 years of age used single dose vaccination regimens; the current submission involves multidose regimens. Experience with other infant vaccinations created a precedent and an expectation that multiple doses of inactivated vaccines would be required to induce adequate antibody responses in infants. Subsequently, the results observed after the first of a 2 dose infant/toddler series in Studies V59P7 and V59P9 indicated that an additional dose would provide a substantial increase in the proportion of subjects achieving hSBA \geq 1:8 and in the short-term persistence of bactericidal antibodies. Based on these considerations and a Phase II study specifically examining immunogenicity in infants (V59P5), it was decided that the proposed primary regimen for young infants would be a 4 dose schedule at 2, 4, and 6 months of age, with a fourth dose to be administered in the second year of life. The proposed catch-up dosing regimen for immunologically naïve older infants (\geq 6 months of age) would be 2 doses, separated by at least 2 months, with the second dose given in the second year of life.

Efficacy

Studies providing efficacy data

The studies submitted in this dossier include pivotal immunogenicity and safety studies in infants and toddlers <2 years are V59P14, V59_33, V59P21, and pivotal safety Study V59P23 and supportive studies V59P5, V59P7, V59P8 (safety only), and V59P9. These are summarised in a table (see Attachment 2). The pivotal immunogenicity and safety study supporting the 2 to 10 year age group is Study V59P20 a Phase III, randomised, observer-blind, multicentre study conducted in the US and Canada in children 2 to 10 years of age to compare the safety and immunogenicity of MenACWY with Menactra.

Evaluator's conclusions on efficacy

Overall, the data presented above support the claim that MenACWY is highly immunogenic in the infant/toddler population; specifically, the 4 dose series proposed for licensure within this application (the first 3 doses at 2, 4, and 6 months of age and a fourth dose in the second year of life) meets the adequacy of immune response criteria predefined by Novartis (GSK) in accordance with feedback obtained from Center for Biologics Evaluation and Research (CBER). Collectively, from these studies, the data also support the claim that the first 3 doses of MenACWY can be administered concomitantly with diphtheria, tetanus, and whooping cough (pertussis) (DTaP), Haemophilus influenzae type b (Hib), Hepatitis B virus (HBV), Inactivated Poliovirus Vaccine (IPV), and cross-reacting material (CRM) containing pneumococcal vaccines (Prennar and Prennar 13) at 2, 4, and 6 months of age without risk of interference. Similar, data from the two dose studies and Study V50P20 supports the immunogenicity of the two dose course in children 2 to 10 years of age.

Safety

Studies providing safety data

When the licensing submission for MenACWY was first prepared in the US, there were some concerns about the integrity and consistency of some of the safety data because of the way it had been collected. They felt that in some sites the worksheets were altered by adding in recall at visits. So after initial review and meetings, an agreement on the size and composition of the infant safety database was made between CBER and Novartis; CBER reiterated their end-of-phase 2 (EOP2) guidance² on the requirement to provide adequate infant safety data for licensure that:

- a) 'Detailed' safety data (that is, including local and systemic reactogenicity) be collected from 3000 randomised controlled subjects receiving the intended infant schedule with US licensed vaccines;
- b) Safety is assessed for 6 months following the final dose in the series;
- c) 50% or more of the safety database is from US infants;
- d) Additional extended safety data (serious adverse events (SAE) and medically significant events) be collected from a further 3000 infants.

Based on the data available at the time, CBER and Novartis agreed on the number of infants from Study V59P14 that were considered adequately controlled for 'detailed safety'. Over the next several months, CBER and Novartis came to an agreement on the design and conduct of a study which would appropriately supplement Study V59P14 to meet CBER's expectations for the detailed safety database. To achieve this, the planned extended safety data Study V59P23 was amended to collect additional detailed safety data from 1840 infants, 1380 of whom would receive MenACWY in a 4 dose series. CBER requested the total database of extended safety subjects be expanded to 4000 MenACWY recipients and that full enrolment of V59P23 be complete at the time of an infant submission.

Pivotal studies that assessed safety as the sole primary outcome

Study V59 P23 was a Phase IIIb, Open-Label, Randomised, Parallel-Group, Multi-Center study to evaluate the safety of Novartis MenACWY Conjugate vaccine when administered with routine infant vaccinations to healthy infants.

² Guidance for Industry Formal Meetings Between the FDA and Sponsors or Applicants

Pivotal and/or main efficacy studies

Studies V59P14 and V59P_33 are described in Section 7 in Attachment 2. These along with V59P23 provide the bulk of the safety data in infants. V59P20 and V59P8 provide much of the data in children 2 to 10.

Other studies

Other efficacy studies

Studies V59P5 and V59P9 also provide safety data as detailed below.

Patient exposure

Between studies V59P14, V59P23, and V59_33, the safety database now includes 9171 infants from 2 months of age exposed to at least one dose of MenACWY (as either a 3-dose or 4 dose series Table 1), of whom 3466 provided detailed safety data through one month post-dose 4. All subjects were to be followed for 6 months postdose 4. Across the 3 studies, US subjects contributed 55% of the detailed safety data, and 44% of all safety data through dose 4.

The Menveo Metadata Collection (MMC) project was specifically designed to assess the accuracy, reliability, and verifiability of safety data collected in the 3 pivotal studies and included 7740 subjects. The data collected in the MMC project enabled Novartis to provide additional analyses of these data that showed the original data included in the submission to be complete, reliable and verifiable. The MMC project showed that the sites, with the exception of one, conducted the 3 pivotal studies according to International Conference on Harmonization (ICH) and GCP.

Nineteen hundred and eighty five (1985) older infants/toddlers (referred to as 'catch-ups') 6 months to 12 months of age at enrolment are included in the safety population for a 2 dose series of MenACWY, of which 1841 received 2 doses (see Table 2). In addition to the pooled population, per a request from CBER, the infant data is also presented for US subjects (4093 MenACWY subjects and 1540 control subjects) and non-US subjects (4642 MenACWY subjects and 1324 control subjects). The pooled analysis of adverse reactions after the first/single meningococcal vaccination in the overall 2 to 10 years age group was performed in 3107 MenACWY subjects (Studies V59P7, V59P8, V59P10, and V59P20), 1255 Menactra subjects (Study V59P20), and 861 Menomune subjects (Studies V59P8 and V59P10) (see Tables 26-29 in Attachment 2).

Table 1: Number of Subjects from Each Study Contributing to Unsolicited Adverse Event tables by Time Period, for Infants

Study group ^a	Infant Series		Between infant series and toddler dose		1 month after first toddler dose		6-month follow-up beginning 1 month after last toddler dose	
	ACWY	Control	ACWY	Control	ACWY	Control	ACWY	Control
V59P14 4-dose (US)	995	504	887	424	820	263	820	179
V59P14 4-dose (non-US)	1725	1007	1620	945	1555	348	1555	175
V59P14 3-dose (non-US)	301	0	301	0	289	0	289	0
V59P23 (US)	2843	997	2613	910	2447	835	2382	810
V59P23 (non-US)	2917	971	2816	946	2770	929	2746	928
V59_33 (US)	255	270	232	243	220	225	213	204
V59P5 (non-US)	135	0	135	0	129	0	125	0
Total	9171	3749	8604	3468	8230	2600	8130	2296
Total 4-dose	8735	3749	8168	3468	7812	2600	7716	2296
Total 4-dose (US)	4093	1771	3732	1577	3487	1323	3415	1193
Total 4-dose (non-US)	4642	1978	4436	1891	4325	1277	4301	1103

Table 2: Summary of Toddler Safety Populations Included in this submission, Catch-up Subjects

Study	2-dose catch-ups	1-dose
V59P8 ^a	0	289
V59P9 ^b	64	56
V59P14 ^{c,d,e}	921	0
V59P21 ^f	1000	0
Total	1985	345

a V59P8: a single dose given alone at 12 to 23 months of age or a single dose given with Prevnar at 12 to 15 months or DTaP at 16 to 23 months of age. b V59P9: 2 doses given at 6 and 12 months of age; 6-month dose was concomitant with Pentacel and Prevnar and 12-month dose was given with Prevnar. c V59P14: Includes study groups US2, US4a, US4b, LA2, LA4, LA6a, and LA6b (groups described in ISE: section 2.1). d Control subjects during the infant series who had visits where they were to receive MenACWY during their toddler year at either 12 and 15 months of age or 13 and 15 months of age. The 12-month dose was given concomitantly with ProQuad, Prevnar, and Havrix.

Postmarketing data

There are 4 post-marketing studies completed, reports submitted late (April 2017). These are briefly summarised under Postmarketing in Attachment 2.

Evaluator's conclusions on safety

Overall, MenACWY has an acceptable safety profile in infants and toddlers 2 to 23 months of age based on data from 8735 infants enrolled to receive the 4 dose infant series and 1985 older infants and toddlers receiving MenACWY. The majority of local and systemic AEs reported after MenACWY occurred within the first 3 days post vaccination; they were mostly of mild to moderate severity and transient duration. Overall, the frequency and character of the unsolicited AEs were similar between MenACWY and control groups. The majority of local and systemic AEs reported after MenACWY occurred within the first 3 days post vaccination; they were mostly of mild to moderate severity and transient duration.

The overall MenACWY reactogenicity profile tended to be comparable to that observed for the US licensed conjugate vaccine, Menactra; MenACWY appeared to be slightly more reactogenic than the US licensed polysaccharide comparator Menomune (particularly the incidence of severe erythema (of transient duration, usually less than 3 days). The majority of local and systemic reactions reported after MenACWY occurred within the first 3 days postvaccination; they were mostly of mild to moderate severity and transient duration. Study P59_340B found an increased risk of Bell's palsy after MenACWY, especially when combined with other routine vaccinations and this association needs further investigation.

First Round Benefit-Risk Assessment

First round assessment of benefits

Indication	
Benefits	Strengths and Uncertainties
Prevention of invasive meningococcal disease in infants (<2) and children 2 to 10 years.	In infants and toddlers, aged 2 to 23 months, MenACWY has been shown to be highly immunogenic in infants, with a high proportion of subjects achieving hSBA \geq 1:8

Indication	
Benefits	Strengths and Uncertainties
Acceptable safety profile	<p>for all serogroups using a validated bactericidal antibody assay after a 4 dose series beginning from 2 months of age or as a 2 dose catch-up series beginning from 6 months of age. In Study V59P14 and Study V59_33, the predefined success criteria for the proportion of subjects with hSBA \geq 1:8 post-dose 4 were met for all serogroups.</p> <p>The post-dose 4 success criteria for the proportion of subjects with hSBA \geq 1:8 were met when applied to 2 dose catch-up series from 2 Phase III studies (V59P14 and V59P21).</p> <p>In children, aged 2 to 10 years, MenACWY has been shown to elicit statistically higher immune responses than quadrivalent polysaccharide meningococcal vaccines for all four serogroups, and non-inferior to the licensed quadrivalent conjugate vaccine Menactra.</p> <p>Statistical definition of non-inferiority was not met in the 2 to 5 and 6 to 10 age groups for serogroup A, when compared to Menactra but was seen in the overall 2 to 10 age group.</p> <p>Two major risks relate to the immunity against serotype C, especially in relation to currently available monovalent C vaccines available for infants. One risk is that this quadrivalent vaccine is not quite as immunogenic against serogroup C and the second, is that there is a dip in immunity prior to the 4 dose (12 months) during which children would be less protected than by the monovalent C vaccine.</p> <p>The safety database includes 8735 infants who were randomised to receive a 4 dose series of MenACWY, as well as 1985 older infants and toddlers to support a 2 dose catch-up series, the vaccine has been shown to be well tolerated with acceptable local and systemic reactogenicity. Reactogenicity probably slightly higher than Menomune (polysaccharide vaccine) and similar to other licensed conjugate vaccine (Menactra).</p> <p>A recorded incidence of Kawasaki disease in the study population, which is difficult to ascertain whether it is equivalent to that in other similar vaccine populations (and also whether it is similar to non-study paediatric populations). So needs to continue to be examined in post-marketing data.</p>

First round assessment of risks

Risks	Strengths and Uncertainties
Statistically higher responses followed MenACWY compared with Menactra for serogroups W and Y, C was non-inferior but in the groups 2-5 and 6-	Currently serogroup A disease is extremely rare in Australia but if other serogroup disease was reduced, there is a possibility of 'gap' filling if the immunity against this serogroup is not as strong.

Risks	Strengths and Uncertainties
<p>10, the response to serogroup A was inferior (but not when the groups were combined).</p> <p>Unexpected serious adverse events; in particular Kawasaki disease was identified in 5 children who received MenACWY (within 30 days).</p>	<p>The company did an analysis on similar groups of children in their other pre-licensure studies and found a similar incidence of Kawasaki disease in both the study and the control arms of these. They argue that there is probably a similar incidence in the community but it is not as well diagnosed or documented.</p>

First round assessment of benefit-risk balance

The benefit-risk balance of MenACWY for the proposed usage is currently favourable with a few caveats.

First Round Recommendation Regarding Authorisation

The evaluator recommended authorisation of this vaccine for prevention of meningococcal infection in children 2 months and over, with the proviso that any further post-marketing data from studies and populations where it is now being used in this population are forwarded for assessment. More post-marketing data is needed for rare immunological events (including Kawasaki disease) and also Bell's palsy.

Some further (possible epidemiological) data/modelling would be useful to see if there is any break-through or gap filling with serogroup C disease in places where there is significant uptake of this vaccine in comparison to a monovalent C vaccine in infants, given the concerns raised about it being less immunogenic in Study V59P22 (not included in this submission). In many countries this vaccine has already replaced the Conjugate C vaccine in the recommended adolescent vaccination.

Clinical Questions/Second Round Evaluation of clinical data submitted in response to questions

The sponsor's response to this evaluation report was considered by the Delegate and addressed in the Delegate's Overview (see Overall conclusions and Risk benefit analysis below).

V. Pharmacovigilance findings

Risk management plan

- GlaxoSmithKline Australia Pty Ltd has submitted EU-RMP version 8.2 (18 April 2016; DLP 14 March 2014) and ASA version 1.0 (initial version dated 21 February 2017, updated version provided with the sponsor's response dated 26 April 2017). This is the first evaluation of the risk management plan for Menveo by TGA.
- The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below in Table 3:

Table 3: Summary of safety concerns

R=routine and A=additional

Summary of safety concerns EU-RMP v8.2 with ASA v1.0		Pharmacovigilance		Risk Minimisation
		R	A	Routine only
No important identified risks				
Important potential risks	Guillain-Barré syndrome	Ü*	Ü†	Ü §
	Acute disseminated encephalomyelitis	Ü*	Ü†	-
	Thrombocytopenia	Ü	Ü†	Ü
	Vasculitis including Kawasaki disease	Ü*	Ü	-
	Brachial neuritis	Ü	Ü†	-
	Facial Paresis	Ü	Ü	-
	Severe injection site reactions	Ü	Ü	-
	Systemic reactions (severe), including febrile convulsion	Ü	Ü	-
	Vaccination failure (lack of efficacy)	Ü	Ü	-
Missing information	Safety during pregnancy or lactation	Ü	?	Ü
	Safety in altered immunocompetence subjects	Ü	-	Ü
	Safety in bleeding disorder patients	Ü	-	Ü
	Safety in serious acute, chronic or progressive disease patients	Ü	-	-
	Safety in subjects with a history of Guillain-Barré syndrome	Ü	-	-
	Exposure to repeated doses, including booster	Ü	Ü‡	-
<p>Missing information: 'Safety and immunogenicity data in elderly subjects (above 65 years of age)' is included in the EU-RMP and not in the ASA.</p> <p>The following safety concerns (struck through above) are proposed to be removed in the sponsor's response:</p> <p>Important potential risk: 'Systemic reactions (severe) including febrile convulsion'</p> <p>Missing information: 'Exposure to repeated doses, including booster'</p> <p>Key: * targeted follow up questionnaires, § Australian only routine risk minimisation, † Completed studies (V59_540B, V59_340B) ‡ Completed studies (V59_57, V59P20E1) ? Pregnancy 'Post marketing Surveillance' – Inadequately described.</p>				

- Ongoing pharmacovigilance activities include:
 - Routine pharmacovigilance with limited use of targeted follow-up questionnaires

- Study V59_740B: Post-licensure observational safety surveillance study of quadrivalent meningococcal ACWY conjugate vaccine MenACWY-CRM (Menveo®) in children *2 months through 23 months of age*. (US)
- Post market surveillance of exposure in pregnancy is proposed including enhanced routine pharmacovigilance with structured follow-up. However, the status of the sponsor's proposed pregnancy surveillance studies is unclear and must be clarified in an update to the RMP.
 - § Study V59_040B [to be closed due to non-recruitment, EU-RMP III.5.2 Table 32]
 - § Study V59_720B [noted by ACV to have failed to enrol any patients in the PBRER]
- Routine risk minimisation activities only are proposed. This is acceptable, given that the product has been used previously in this age group in line with official recommendations.

Second round evaluation

New and outstanding recommendations

The Risk Management Plan is acceptable; however, the three (3) minor recommendations below should be addressed in a post approval update. In addition, there are two recommendations for the Delegate's consideration (see Advice to the Delegate, below).

Recommendation 11 The sponsor must submit the draft revised EU-RMP and final agreed revised EU-RMP with an appropriately updated ASA. These should include the changes proposed in the response and updated pharmacovigilance plan which must clarify the status of ongoing studies including V59_720B.

Recommendation 12 The structured follow-up of adverse event reports should collect appropriate ethnic demographic information for Australia. This must include Australian indigenous identity (ATSI) categories as follows: Aboriginal, Torres Strait Islander, Aboriginal and Torres Strait Islander, 'Neither'.

Recommendation 13 The sponsor should adequately address the following advice from the resolution of the Advisory Committee on Vaccines and update the risk management plan accordingly:

'The committee queried the status of post-marketing surveillance of administration of the vaccine during pregnancy (V59_720B); the Periodic Benefit Risk Evaluation Report stated that the study seeks to enrol 100 exposed pregnancies over a three-year period starting 30 September 2014 but that nil women had been enrolled as at February 2016.'

'The utility of the targeted follow-up questionnaire for acute disseminated encephalomyelitis, Guillain-Barre syndrome and vasculitis/Kawasaki syndrome was unclear, but the signals did not seem to justify an active surveillance program at this time.'

'The ACV noted the surveillance data on vaccine failures provided by the sponsor in its pre-ACV response, and recommended that capture of vaccine failure data for the extended schedules in infants should be part of pharmacovigilance activities.'

'Targeted long-term follow-up studies of persistence of immunity should be required.'

Advice to the Delegate

The Delegate is requested to consider the following comments on the Product information

- The PI should include a statement on Serogroup A immune response persistence [RMP recommendation, supported in the Resolution of ACV].
- Important potential risks which are observed rare adverse events (such as Acute disseminated encephalomyelitis (ADEM) and Guillain-Barré Syndrome (GBS)) should be listed in the PI: 'Adverse Events' section.

Wording for conditions of registration

[Amended on 21 June 2017, to correctly reference the ASA dated 26 April 2017]

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

1. Implement the Menveo EU-RMP version 8.2, 18 April 2016 (data lock point 14 March 2014) with Australian Specific Annex version 1.0, 26 April 2017 submitted with PM-2017-00536-1-2, to be revised to the satisfaction of the TGA, and any future updates as a condition of registration.
2. The sponsor has committed to providing the TGA with the soon to be agreed, revised EU-RMP. The ASA should also be updated accordingly, as agreed.VI.

Overall conclusion and risk/benefit assessment

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

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

This Overview captures salient data/studies from this submission for the attention of the ACV. For full details, please refer to the accompanying TGA clinical evaluation report (CER; Attachment 2). Studies V59_33 and V59P14 are pivotal data supporting the 4 dose infant series. Study V59P21 is the pivotal study supporting the 2 dose catch-up schedule in infants 7-23 months of age. Study V59P20 is pivotal study for single dose recommendation in 2 to 10 years of age group. Study V59P23 was a safety study in the 4 dose recipient infants. These studies were controlled, randomised, open-label trials in healthy infant/toddler/children population.

The main design features of these studies are presented in the Tables 4-7 below:

Table 4: Study V59P14 (early study with multiple treatment arms; US and LA cohorts)

Study Number	Geographic Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Exposed	Healthy Subjects or Diagnosis of Patient	Number of MenACWY Injections
V59P14	US	Safety and Immune Response of MenACWY given with US Routine Infant Vaccines vs Routine Infant Vaccines Alone with one or two Doses MenACWY in 2 nd Year of Life	Open-Label, Randomized	MenACWY 10-5-5-5µg Ad-IM (+ Routine Vaccines)	3035	Healthy Subjects	Two or Three in Infants
	Argentina Colombia		Phase 3 Multi-Center	Routine Vaccines Only Followed by MenACWY 10-5-5-5µg Ad- IM	1521	Infants 2 m	One or Two in Toddlers

Table 5: Study V59_33 (subsequent 4 dose pivotal study in infants)

Objectives of the Study	Study Design and Type of Control	Subjects' Ages at Enrolment; Geographic Location	Study Group	Test Products		Number of Subjects Enrolled
				MenACWY Vaccination Schedule (Months of Age)	Routine Vaccination Schedule (Months of Age)	
V59_33						
Assessment of immunogenicity: MenACWY: 4-dose series, immunogenicity including persistence, and concomitant use with other routine pediatric vaccines Assessment of safety/tolerability	Randomized, open-label, multicenter	2 months; US, Australia, Canada	MenACWY+Routine vaccines (MenACWY+R)	2, 4, 6, 12	2, 4, 6, 12	258
			Routine vaccine only (Routine)	None	2, 4, 6, 12	271

Table 6: Study V59P21 (2 dose catch-up study in 7, 12-23 month old infants)

Objectives of the Study	Study Design and Type of Control	Subjects' Ages at Enrolment; Geographic Location	Study Group	Test Products		Number of Subjects Enrolled
				MenACWY Vaccination Schedule (Months of Age)	Routine Vaccination Schedule (Months of Age)	
V59P21						
Assessment of immunogenicity: MenACWY: 2-dose series, immunogenicity including concomitant use with routine toddler MMRV vaccine Assessment of safety/tolerability	Randomized, open-label, multicenter	7 to 9 months US	MenACWY+MMRV (ACWY+MMRV)	7 to 9, 12	12	504
			MenACWY→MMRV (ACWY)	7 to 9, 12	13.5	510
		12 months* US	MMRV	None	12	616

Table 7: Study V59P20 (active comparator controlled, single dose study in 2 to 10 years old children)

Study Number	Geographic Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Exposed	Healthy Subjects or Diagnosis of Patient	Number of MenACWY Injections
V59P20	US Canada	Safety and Immune response to MenACWY vs Menactra™	Observer-Blind, Randomized, Active Controlled Phase 3 Multi-Center	MenACWY 10-5-5-5µg Ad-IM Menactra™	1635 1263	Healthy Subjects Children 2-10 y	One or Two

Results of Immunogenicity- ACWY

Study V5914: One month after completion of 4 dose series (at 2, 4, 6, 12 months of age - US cohort), the percentage of subjects with hSBA \geq 1:8 ranged from 94% to 100% across

the 4 serotypes with LL of 95%CI of 87%, 92%, 96% and 96% for serotypes A, C, W and Y respectively.

One month after completion of 4 dose series (at 2, 4, 6, 16 months of age – LA cohort), the percentage of subjects with hSBA \geq 1:8 ranged from 95% to 100% across the 4 serotypes with LL of 95%CI of 89%, 94%, 97% and 95% for serotypes A, C, W and Y respectively.

Study V59_33: One month after completion of 4 dose series (at 2, 4, 6, 12 months of age), the percentage of subjects with hSBA \geq 1:8 ranged from 89% to 97% across the 4 serotypes with LL of 95%CI of 83%, 90%, 93% and 92% for serotypes A, C, W and Y respectively.

Study V59P21: One month after completion of 2 dose series (at 7-9 and at 12 months of age), the percentage of subjects with hSBA \geq 1:8 ranged from 88% to 100% across the 4 serotypes with LL of 95%CI of 84%, 98%, 96% and 93% for serotypes A, C, W and Y respectively.

Table 8: Percentage of subjects with hSBA \geq 1:8 at 1 month after completing the age specific MenACWY vaccination schedule. Studies V59_33, V59P14, V59P9, V59P7 and V59P13

Sero-group	4-Dose Series V59_33 ^a	4-Dose Series US Infants V59P14 ^a	4-Dose Series LA Infants V59P14 ^b	2-Dose Catch-up Series				Single Dose (Adolescent and Adults) V59P13	
				Older Infants V59P21 ^c	Older Infants V59P9 ^d	Toddlers V59P14 ^e	Toddlers V59P7 ^f	MenACWY	Menactra
A	N=168 89% (83%*, 93%)	N=84 94% (87%*, 98%)	N=120 95% (89%*, 98%)	N=379 88% (84%*, 91%)	N=50 84% (71%, 93%)	N=101 97% (92%, 99%)	N=29 86% (68%, 96%)	N=2038 72% (70%, 74%)	N=680 69% (65%, 72%)
C	N=156 95% (90%*, 98%)	N=86 98% (92%*, 100%)	N=122 98% (94%, 100%)	N=195 100% (98%*, 100%)	N=55 100% (94%, 100%)	N=102 100% (96%, 100%)	N=29 100% (88%, 100%)	N=2444 83% (81%, 84%)	N=819 79% (76%, 82%)
W	N=153 97% (93%*, 99%)	N=85 100% (96%*, 100%)	N=112 100% (97%, 100%)	N=196 98% (96%*, 100%)	N=40 100% (91%, 100%)	N=98 100% (96%, 100%)	N=29 100% (88%, 100%)	N=1508 95% (94%, 96%)	N=580 89% (86%, 91%)
Y	N=153 96% (92%*, 99%)	N=84 100% (96%*, 100%)	N=109 99% (95%, 100%)	N=198 96% (93%*, 99%)	N=53 100% (93%, 100%)	N=95 100% (96%, 100%)	N=29 100% (88%, 100%)	N=1539 85% (83%, 87%)	N=600 70% (66%, 73%)

* study-specific predefined statistical criterion for demonstrating adequacy of the immune response met.

^a at 2, 4, 6, and 12 months of age (V59_33 study group MenACWY-R and V59P14 study group US1A).

^b at 2, 4, 6, and 16 months of age (V59P14 study group LA3A).

^c 2-dose schedule at 7-9 months of age and 12 months of age.

^d 2-dose schedule at 6 and 12 months of age.

^e 2-dose schedule at 12 and 15 months of age (V59P14 study group LA4).

^f 2nd dose administered 6 months after the 1st dose.

Table 8 above also shows results of 2 dose series in other studies/study arms as well as historical comparison with the currently approved age group (single dose in adolescents and adults).

For the 4 dose series in infants, results of ‘% with hSBA \geq 1:8’ at various time-points from multiples arms of the Study V59P14 (US and Latin American (LA) groups) and the Study V59_33 were indicative of good immune response post Dose 3 but in all instances the pre Dose 4 levels showed precipitous drop in seroprotection levels as shown below in Table 9 which also includes GMT data:

Table 9: Percentage of subjects (95% CI) with hSBA ≥1:8 GMTs (95% CI) at baseline, Post 3rd and Pre and Post 4th dose, MenACWY 4 dose series Studies V59_33 and V59P14

Sero-group	2, 4, 6, 12 months of age								2, 4, 6, 16 months of age			
	V59P14 US				V59_33				V59P14 LA			
	US1 Baseline	US1 Post 3 rd dose	US1A Pre 4 th dose	US1A Post 4 th dose	Baseline	Post 3 rd dose	Pre 4 th dose	Post 4 th dose	LA3 Baseline	LA3 Post 3 rd dose	LA3A Pre 4 th dose	LA3A Post 4 th dose
A	N=177	N=212	N=84	N=84	N=170	N=202	N=168	N=168	N=271	N=268	N=120	N=120
≥1:8	2% (0, 5%)	67% (61%, 74%)	10% (4%, 18%)	94% (87%*, 98%)	2% (0, 5%)	76% (69%, 81%)	7% (4%, 12%)	89% (83%*, 93%)	0 (0, 2%)	89% (85%, 93%)	13% (8%, 21%)	95% (89%, 98%)
GMTs	2.11 (2, 2.23)	13 (11, 16)	2.51 (2.14, 2.96)	77 (55, 109)	2.09 (2, 2.18)	21 (17, 26)	2.52 (2.26, 2.82)	54 (44, 67)	2.03 (1.97, 2.09)	43 (36, 52)	2.95 (2.57, 3.39)	146 (113, 188)
C	N=168	N=204	N=86	N=86	N=166	N=199	N=156	N=156	N=272	N=272	N=122	N=122
≥1:8	7% (3%, 11%)	97% (93%, 99%)	50% (39%, 61%)	98% (92%*, 100%)	7% (3%, 12%)	94% (90%, 97%)	37% (30%, 45%)	95% (90%*, 98%)	4% (2%, 8%)	97% (94%, 99%)	22% (15%, 31%)	98% (94%, 100%)
GMTs	2.48 (2.23, 2.75)	108 (92, 127)	7.72 (5.9, 10)	227 (155, 332)	2.49 (2.25, 2.76)	74 (62, 87)	5.98 (4.81, 7.43)	135 (107, 171)	2.34 (2.19, 2.49)	150 (127, 177)	3.83 (3.2, 4.6)	283 (225, 355)
W	N=165	N=197	N=85	N=85	N=152	N=194	N=153	N=153	N=261	N=264	N=112	N=112
≥1:8	17% (12%, 24%)	96% (93%, 99%)	71% (60%, 80%)	100% (96%*, 100%)	13% (8%, 20%)	98% (95%, 99%)	70% (62%, 77%)	97% (93%*, 99%)	10% (7%, 14%)	98% (96%, 100%)	62% (52%, 71%)	100% (97%, 100%)
GMTs	3.07 (2.7, 3.5)	100 (86, 116)	14 (11, 18)	416 (288, 602)	2.94 (2.52, 3.43)	79 (67, 92)	15 (12, 18)	215 (167, 227)	2.54 (2.31, 2.79)	182 (159, 208)	13 (11, 16)	727 (586, 903)
Y	N=150	N=182	N=84	N=84	N=144	N=188	N=153	N=153	N=260	N=263	N=109	N=109
≥1:8	5% (2%, 10%)	96% (92%, 98%)	61% (49%, 71%)	100% (96%*, 100%)	8% (4%, 13%)	94% (89%, 97%)	53% (45%, 61%)	96% (92%*, 99%)	3% (2%, 6%)	98% (96%, 99%)	47% (37%, 57%)	99% (95%, 100%)
GMTs	2.53 (2.31, 2.77)	73 (62, 86)	11 (8.76, 15)	395 (269, 580)	2.52 (2.28, 2.77)	51 (43, 61)	8.39 (6.9, 10)	185 (148, 233)	2.26 (2.14, 2.39)	125 (107, 146)	8.1 (6.58, 9.96)	590 (463, 751)

* pre-specified statistical criteria met (V59P14 US cohorts: LL of the 95% CI ≥ 80% for serogroup A and ≥ 85% for serogroups C, W, and Y; V59_33: LL of the 95% CI > 80% for serogroup A and > 85% for serogroups C, W, and Y; there were no pre-specified statistical criteria for adequacy of the immune response for the LA cohorts of study V59P14).

Study V59P20: Immunogenic non-inferiority ('% with hSBA ≥ 1:8') was demonstrated between a single dose of Menveo and a single dose of Menactra in healthy children 2 to 10 years of age according to the predefined criterion (LL95%CI no worse than -10% for the group difference), although for serotype A the result was marginal and statistically significant (-6% [95%CI -9.0%, -2.0%]) that is, interval fell below zero. The age stratified results (2-5 years of age and 6-10 years of age) could not demonstrate non-inferiority for serotype A that is, LL95%CI breached -10% limit in both strata:

Table 10: Study V59P20: Menveo versus Menactra ACWY immunogenicity – one month after vaccination in children 2 to 10 years of age (single dose schedule)

Endpoint by Serogroup	2-5			6-10			2-10		
	Menveo (95% CI)	Menactra (95% CI)	Percent Difference (Menveo – Menactra) or GMT ratio (Menveo/ Menactra) (95% CI)	Menveo (95% CI)	Menactra (95% CI)	Percent Difference (Menveo – Menactra) or GMT ratio (Menveo/ Menactra) (95% CI)	Menveo (95% CI)	Menactra (95% CI)	Percent Difference (Menveo – Menactra) or GMT ratio (Menveo/ Menactra) (95% CI)
A	N=606	N=611		N=551	N=541		N=1157	N=1152	
% Seroreponse [‡]	72 (68, 75)	77 (73, 80)	-5 (-10.0, -0.3)	77 (73, 80)	83 (79, 86)	-6 (-11, -1)	74 (71, 76)	80 (77, 82)	-6* (-9, -2)
% _{≥1:8}	72 (68, 75)	78 (74, 81)	-6 (-11, -1)	77 (74, 81)	83 (80, 86)	-6 (-11, -1)	75 (72, 77)	80 (78, 83)	-6* (-9, -3)
GMT	26 (22, 30)	25 (21, 29)	1.04* (0.86, 1.27)	35 (29, 42)	35 (29, 41)	1.01* (0.83, 1.24)	30 (27, 34)	29 (26, 33)	1.03* (0.89, 1.18)
C	N=607	N=615		N=554	N=539		N=1161	N=1154	
% Seroreponse [‡]	60 (56, 64)	56 (52, 60)	4* (-2, 9)	63 (59, 67)	57 (53, 62)	6* (0, 11)	61 (58, 64)	57 (54, 60)	5* [§] (1, 9)
% _{≥1:8}	68 (64, 72)	64 (60, 68)	4* (-1, 10)	77 (73, 80)	74 (70, 77)	3* (-2, 8)	72 (70, 75)	68 (66, 71)	4* (0, 8)
GMT	18 (15, 20)	13 (11, 15)	1.33* [§] (1.11, 1.6)	36 (29, 45)	27 (21, 33)	1.36* [§] (1.06, 1.73)	23 (21, 27)	17 (15, 20)	1.34* [§] (1.15, 1.56)
W-135	N=594	N=605		N=542	N=533		N=1136	N=1138	
% Seroreponse [‡]	72 (68, 75)	58 (54, 62)	14* [§] (9, 19)	57 (53, 61)	44 (40, 49)	13* [§] (7, 18)	65 (62, 67)	51 (48, 54)	13* [§] (9, 17)
% _{≥1:8}	90 (87, 92)	75 (71, 78)	15* [§] (11, 19)	91 (88, 93)	84 (81, 87)	7* [§] (3, 11)	90 (88, 92)	79 (77, 81)	11* [§] (8, 14)
GMT	43 (38, 50)	21 (19, 25)	2.02* [§] (1.71, 2.39)	61 (52, 72)	35 (30, 42)	1.72* [§] (1.44, 2.06)	49 (44, 54)	26 (23, 29)	1.87* [§] (1.65, 2.12)
Y	N=593	N=600		N=545	N=539		N=1138	N=1139	
% Seroreponse [‡]	66 (62, 70)	45 (41, 49)	21* [§] (16, 27)	58 (54, 62)	39 (35, 44)	19* [§] (13, 24)	62 (60, 65)	42 (40, 45)	20* [§] (16, 24)
% _{≥1:8}	76 (72, 79)	57 (53, 61)	19* [§] (14, 24)	79 (76, 83)	63 (59, 67)	16* [§] (11, 21)	77 (75, 80)	60 (57, 63)	18* [§] (14, 21)
GMT	24 (20, 28)	10 (8.68, 12)	2.36* [§] (1.95, 2.85)	34 (28, 41)	14 (12, 17)	2.41* [§] (1.95, 2.97)	29 (25, 32)	12 (11, 14)	2.37* [§] (2.06, 2.73)

[‡] Seroreponse was defined as: a) post vaccination hSBA $\geq 1:8$ for subjects with a pre-vaccination hSBA $< 1:4$; or, b) at least 4-fold higher than baseline titers for subjects with a pre-vaccination hSBA $\geq 1:4$.

* Non-inferiority criterion met (the lower limit of the two-sided 95% CI $> -10\%$ for vaccine group differences [Menveo minus Menactra] and > 0.5 for ratio of GMTs [Menveo/Menactra]).

§ Immune response was statistically higher (the lower limit of the two-sided 95% CI $> 0\%$ for vaccine group differences or > 1.0 for ratio of GMTs); however the clinical relevance of higher post-vaccination immune responses is not known

The sponsor's response to the CER indicates that Menactra licensed in the US and Canada may be a polysaccharide vaccine in which case this study can only be meaningfully interpreted as a single arm (uncontrolled) study. The sponsor is requested to please confirm whether Menactra used in this study was a conjugate or a polysaccharide formulation.

This study also sought to explore immune response in a subgroup of 2-5 years of age after a second dose of Menveo given at least 2 months after the first dose of Menveo. These results are provided in Table 11 below:

Table 11: Study V59P20: Percentage of Subjects with hSBA titres \geq 1:8 and GMTs of Subjects at Day 1 and at One Month Post-Vaccination, Children 2 to 5 years of age (2 doses versus 1dose)

	hSBA Titer \geq 1:8			Seroresponse			GMTs			
	MenACWY 2 Doses	MenACWY 1 Dose	P-Value	MenACWY 2 Doses	MenACWY 1 Dose	P-Value	MenACWY 2 Doses	MenACWY 1 Dose	P-Value	
Day 1	A ^a	4 (1%) (0-3)	9 (1%) (1-3)	.86	NA	NA	NA	2.1 (2.02-2.18)	2.1 (2.04-2.16)	.99
	C ^b	27 (9%) (6-13)	61 (10%) (8-13)	.65	NA	NA	NA	2.92 (2.65-3.23)	3.05 (2.83-3.29)	.42
	W ^c	61 (21%) (17-26)	143 (24%) (21-28)	.17	NA	NA	NA	4.07 (3.42-4.84)	4.38 (3.84-5.01)	.43
	Y ^d	26 (9%) (6-13)	81 (14%) (11-17)	.18	NA	NA	NA	2.75 (2.44-3.09)	3 (2.74-3.28)	.16
Day 29	A ^a	266 (91%) (88-94)	436 (72%) (68-75)	<.001***	264 (91%) (87-94)	434 (72%) (68-75)	<.001***	64 (51-81)	27 (23-32)	<.001***
	C ^b	289 (99%) (97-100)	413 (68%) (64-72)	<.001***	286 (98%) (95-99)	363 (60%) (56-64)	<.001***	144 (118-177)	18 (15-21)	<.001***
	W ^c	286 (99%) (98-100)	532 (90%) (87-92)	<.001***	256 (89%) (85-92)	426 (72%) (68-75)	<.001***	132 (111-157)	41 (36-47)	<.001***
	Y ^d	280 (98%) (95-99)	448 (76%) (72-79)	<.001***	271 (95%) (91-97)	394 (66%) (62-70)	<.001***	102 (82-126)	23 (20-27)	<.001***

Source: Table 14.2.1.6, Table 14.2.1.10, Table 14.2.1.18; * p < 0.05, ** p < 0.01, *** p < 0.001, NA = Not applicable.

^a serogroup A: MenACWY 2 Doses N=291, MenACWY 1 Dose N=606

^b serogroup C: MenACWY 2 Doses N=293, MenACWY 1 Dose N=607

^c serogroup W: MenACWY 2 Doses N=288, MenACWY 1 Dose N=594

^d serogroup Y: MenACWY 2 Doses N=286, MenACWY 1 Dose N=593

Results Immunogenicity of Concomitant Vaccines on Concomitant Administration with Menveo

Study V59P14: Concomitant administration of routine infant/toddler vaccines (3 doses at 2, 4, 6 months age) with Menveo did not indicate any interference with immune response for diphtheria, tetanus, polio (type 1, 2, 3), hepatitis B and Hib vaccine antigens.

Non-inferiority (seroresponse) could not be demonstrated for pneumococcal (PnC) antigen 6B (-8% [LL95%CI -14 to -1%]) based on US cohorts.

Immune response to pertussis antigens (PT, FHA, PRN) in terms of GMC was equivalent (non-inferior) with or without Menveo and routine vaccines according to the predefined criterion (geometric mean concentration (GMC) ratio >0.67). However, note that response to PT was statistically significantly lower in the LA cohorts (GMC ratio 0.8 [95%CI 0.66, 0.97]) that is, interval wholly below 1.0.

Study V59_33: Concomitant administration of routine infant/toddler vaccines with Menveo did not indicate any interference with immune response for diphtheria, tetanus, polio (type 1, 2, 3), hepatitis B and Hib vaccine antigens.

Non-inferiority (seroresponse) could not be demonstrated for pneumococcal (PnC) antigens 6B (LL95%CI -10.3%) and 23F (LL95%CI -11.4%). Non-inferiority (seroresponse) could not be demonstrated for pertussis with LL95%CI being -12.1% and -10.6% for PT and FIM antigens respectively. A post-hoc analysis with adjustment of factors was also done for which please see the footnote to Table 12 below.

Pertussis antigens response in terms of GMC ratio was equivalent (non-inferior) for with or without Menveo.

The detailed results (studies V59P14 and V59_33) are provided in Table 12 below:

Table 12: Immune response (95% CI) for concomitant antigen at 1 month after the third dose (7 months of age) Key secondary immunogenicity endpoints, Study V59P14 (US and LA groups) and Study V59_33 (unadjusted analysis)

Antigen	V59P14						V59_33		
	US1 (concom)	US2 (non-concom)	US1 minus US2 (95% CI)	LA3 (concom)	LA4 (non-concom)	LA3 minus LA4 (95% CI)	MenACWY +R (concom)	Routine (non-concom)	MenACWY+R minus Routine (95% CI)
Diphtheria (≥0.1 IU/mL)	N = 214 100% (97%, 100%)	N = 102 100% (96%, 100%)	0 (-3%*, 3%)	N=283 99% (96%, 100%)	N=137 99% (95%, 100%)	0 (-2.3%*, 3.8%)	N=207 99% (96%, 100%)	N=218 99% (96%, 100%)	0 (-2.9%*, 2.6%)
Tetanus (≥0.1 IU/mL)	N = 214 100% (98%, 100%)	N = 102 100% (96%, 100%)	0 (-2%*, 4%)	N=283 100% (99%, 100%)	N=137 100% (97%, 100%)	0% (-1.3%*, 2.7%)	N=207 97% (94%, 99%)	N=218 97% (93%, 99%)	0 (-3.3%*, 3.9%)
Poliovirus Type 1 (≥1 E)	N = 176 99% (97%, 100%)	N = 98 100% (96%, 100%)	-1% (-3%*, 3%)	N=252 99% (97%, 100%)	N=120 98% (94%, 100%)	0% (-2.0%*, 4.7%)	N=115 99% (95%, 100%)	N=113 98% (94%, 100%)	1% (-3.1%*, 5.4%)
Type 2 (≥1 E)	100% (98%, 100%) (N=175)	100% (96%, 100%)	0 (-2%*, 4%)	98% (95%, 99%)	98% (93%, 99%)	0% (-3.0%*, 4.8%)	N=185 100% (98%, 100%)	N=179 99% (97%, 100%)	1% (-1.4%*, 3.0%)
Type 3 (≥1 E)	99% (97%, 100%)	100% (96%, 100%)	-1% (-3%*, 3%)	96% (93%, 98%)	97% (92%, 99%)	-1% (-4.4%*, 4.5%)	N=164 99% (97%, 100%)	N=162 100% (98%, 100%)	-1% (-3.3%*, 1.7%)
HBV (≥10mIU/mL)	N = 148 99% (96%, 100%)	N = 98 100% (96%, 100%)	-1% (-4%*, 3%)	N=237 100% (98%, 100%)	N=118 100% (97%, 100%)	0% (-2.3%*, 2.7%)	N=138 96% (92%, 99%)	N=148 97% (92%, 99%)	0 (-5.2%*, 4.5%)
Hib (≥0.15µg/mL)	N = 213 99% (97%, 100%)	N = 101 100% (96%, 100%)	-1% (-3%*, 3%)	N=283 97% (94%, 99%)	N=137 99% (96, 100)	-2% (-5.3%*, 1.0%)	N=187 95% (90%, 97%)	N=194 89% (84%, 93%)	5% (0*, 11.2%)
PnC (≥0.35µg/mL)	N = 181 98% (95%, 100%)	N = 102 100% (96%, 100%)	-2% (-5%*, 2%)	N=256 97% (94%, 99%)	N=126 98% (94%, 100%)	-1% (-4.2%*, 3.0%)	N=183 99% (96%, 100%)	N=178 98% (94%, 99%)	1% (-1.9%*, 4.6%)
PnC 6B	88% (83%, 93%)	96% (90%, 99%)	-8% (-14%, -1)	91% (87%, 95%) N=255	90% (83%, 94%) N=124	2% (-4.0%*, 9.0%)	86% (80%, 91%)	90% (84%, 94%)	-4% (-10.3%*, 3.2%)
PnC 9V	98% (94%, 99%)	98% (93%, 100%)	0% (-4%*, 5%)	97% (94%, 99%)	96% (91%, 99%)	1% (-2.8%*, 6.0%)	91% (86%, 95%)	94% (90%, 97%)	-3% (-8.7%*, 2.3%)
PnC 14	100% (98%, 100%)	99% (95%, 100%)	1% (-1%*, 5%)	98% (95%, 99%)	98% (94%, 100%)	-1% (-3.7%*, 3.4%)	99% (96%, 100%)	99% (96%, 100%)	0 (-2.8%*, 3.0%)
PnC 18C	97% (94%, 99%)	100% (96%, 100%)	-3% (-6%*, 1%)	95% (91%, 97%)	98% (94%, 100%)	-3% (-7.2%*, 0.8%)	95% (90%, 97%)	97% (94%, 99%)	-3% (-7.3%*, 1.6%)
PnC 19F	99% (96%, 100%)	100% (96%, 100%)	-1% (-4%*, 3%)	98% (96%, 100%) N=254	96% (91%, 99%)	2% (-0.8%*, 7.5%)	100% (98%, 100%)	97% (93%, 99%)	3% (1.3%*, 7.1%)
PnC 23F	92% (87%, 95%)	94% (88%, 98%)	-2% (-8%*, 5%)	95% (91%, 97%)	94% (88%, 97%) N=125	1% (-3.7%*, 7.0%)	89% (83%, 93%)	94% (89%, 97%)	-5% (-11.4%*, 0.9%)
Pertussis seroresponse ^a	Assessment of vaccine group differences by seroresponse for the pertussis antigens was a supportive secondary endpoint in study V59P14 ^b						N=185 77% (71%, 83%)	N=191 81% (75%, 86%)	-4% (-12.1%*, 4.3%)
FHA							70% (63%, 76%)	65% (58%, 72%)	4% (-5.1%*, 13.6%)
PRN							73% (66%, 79%)	73% (66%, 79%)	0 (-8.8%*, 9.1%)
FIM							74% (67%, 80%)	76% (69%, 82%)	-2% (-10.6%*, 6.8%)
Pertussis GMC Ratio	US1	US2	US1:US2 GMC ratio (95% CI)	LA3	LA4	LA3:LA4 GMC ratio (95% CI)	MenACWY +R (concom)	Routine (non-concom)	MenACWY+R minus Routine (95% CI)
PT	N = 174 54 (48, 62)	N = 83 54 (44, 66)	1 (0.79*, 1.26)	N=281 45 (41, 50)	N=135 49 (42, 56)	0.93 (0.78*, 1.1)	N=185 25 (21, 30)	N=191 24 (21, 29)	1.02 (0.81*, 1.28)
FHA	118 (106, 132)	114 (97, 134)	1.03 (0.85*, 1.25)	99 (91, 109)	112 (99, 128)	0.88 (0.75*, 1.03)	48 (43, 54)	47 (42, 52)	1.04 (0.9*, 1.19)
PRN	114 (100, 130)	110 (90, 134)	1.04 (0.83*, 1.32)	119 (106, 133)	149 (127, 175)	0.8 (0.66, 0.97)	56 (47, 65)	54 (46, 62)	1.04 (0.84*, 1.28)
FIM	FIM was not assessed in study V59P14 (Pediarix does not contain FIM)						133 (113, 157)	122 (105, 143)	1.09 (0.88*, 1.35)

concom-concomitant administration, non-concom-non-concomitant administration.
^a statistical criterion for non-inferiority met (LL of the 95% CI around the difference in the percentage of subjects with the antigen-specific threshold response [concomitant minus non-concomitant] > -10%, for pobo 1, 2, and 3 > -5%, LL of the 95% CI around the GMC ratio [concomitant non-concomitant] > 0.67)
^b seroresponse for pertussis antigens was defined as: (i) in unally seroregative infants ≥4 times LLQ; and (ii) in unally seropositive infants at least 4 times increase of prevaccination concentration.
^c an assessment of vaccine group differences by seroresponse for the pertussis antigens (supportive secondary endpoint in study V59P14) are provided in Seq 0064, section 5.3.5.1, CSR V59P14, Table 11.4.1-5B and discussed in the ISE, section 3.2.2.2.1, subsection entitled Pertussis Antigens at Study V59P14
^d after a post-hoc assessment adjusting for center, non-inferiority margins were met, with the LL of the 2-sided 95% CI of -3.9%, -1.8%, and -2.3%, for PT, PnC 6B, and PnC 23F, respectively (CSR V59_33 Appendix 16.1.9.18 and Appendix 16.1.9.20)

GMC analysis of the 7 pneumococcal vaccine antigens was also provided for both studies V59P14 and V59_33 and non-inferiority was claimed on the pre-defined criterion of $LL95\%CI > 0.5$ for the GMC ratio as shown below in Table 13 below:

Table 13: GMCs and GMC ratios (95% CI) of pneumococcal antibodies at 1 month after the 4th dose of Prevnar given at 12 months of age with and without concomitant MenACWY Key secondary immunogenicity end points Studies V59P14 and V59_33

Pneumococcal Antigen	V59P14			V59_33		
	US1A	US1B	US1A:US1B (95% CI)	MenACWY +R	Routine	MenACWY+R:Routine (95% CI)
PnC 4	N = 86 2.9 (2.33, 3.61)	N = 99 3.24 (2.64, 3.97)	0.9 (0.67*, 1.2)	N=161 1.57 (1.35, 1.82)	N=170 1.6 (1.39, 1.85)	0.98 (0.8*, 1.19)
	N = 86 6.82 (5.67, 8.21)	N = 99 8.58 (7.22, 10)		N=161 5.92 (5.05, 6.95)	N=170 7.8 (6.69, 9.09)	
PnC 6B	N = 86 2.8 (2.26, 3.47)	N = 99 3.13 (2.56, 3.82)	0.89 (0.67*, 1.2)	N=161 1.67 (1.44, 1.93)	N=170 1.91 (1.66, 2.19)	0.87 (0.72*, 1.06)
	N = 86 12 (9.74, 14)	N = 99 15 (12, 17)		N=161 7.9 (6.73, 9.28)	N=170 7.61 (6.52, 8.88)	
PnC 14	N = 86 2.76 (2.26, 3.38)	N = 99 2.71 (2.24, 3.27)	1.02 (0.78*, 1.34)	N=161 1.79 (1.55, 2.08)	N=170 1.8 (1.57, 2.08)	0.99 (0.82*, 1.2)
	N = 86 3.63 (3, 4.39)	N = 99 3.48 (2.92, 4.16)		N=161 5.03 (4.36, 5.82)	N = 169 5.68 (4.95, 6.53)	
PnC 18C	N = 86 5.31 (4.2, 6.71)	N = 99 5.63 (4.52, 7.01)	0.94 (0.69*, 1.29)	N=161 3.3 (2.8, 3.89)	N=170 3.91 (3.34, 4.57)	0.84 (0.68*, 1.04)
	N = 86 12 (9.74, 14)	N = 99 15 (12, 17)		N=161 7.9 (6.73, 9.28)	N=170 7.61 (6.52, 8.88)	
PnC 19F	N = 86 2.76 (2.26, 3.38)	N = 99 2.71 (2.24, 3.27)	1.04 (0.81*, 1.34)	N=161 1.79 (1.55, 2.08)	N=170 1.8 (1.57, 2.08)	0.89 (0.73*, 1.07)
	N = 86 5.31 (4.2, 6.71)	N = 99 5.63 (4.52, 7.01)		N=161 3.3 (2.8, 3.89)	N=170 3.91 (3.34, 4.57)	
PnC 23F	N = 86 12 (9.74, 14)	N = 99 15 (12, 17)	0.8 (0.63*, 1.03)	N=161 7.9 (6.73, 9.28)	N=170 7.61 (6.52, 8.88)	1.04 (0.84*, 1.28)
	N = 86 2.76 (2.26, 3.38)	N = 99 2.71 (2.24, 3.27)		N=161 1.79 (1.55, 2.08)	N=170 1.8 (1.57, 2.08)	

* statistical criterion for non-inferiority met (LL of the 95% CI around the GMC ratio [concomitant non-concomitant] > 0.5).

Study V59P21: Concomitant administration of MMRV with Menveo did not indicate interference of immune response:

Table 14: V59P21 Immunogenicity of MMRV with or without concomitant Menveo

		Number (%) of subjects [95% CI]		
		MenACWY + MMRV*	MMRV*	Difference (MenACWY + MMRV* - MMRV*)
Measles seroconversion \geq 255 mIU/mL	Post-dose	N = 350 342 (98%) [96 – 99]	N = 467 462 (99%) [98 – 100]	-1% [-3.4 – 0.5]
		N = 365 357 (98%) [96 – 99]	N = 499 481 (96%) [94 – 98]	1% [-1.0 – 3.7]
Mumps seroconversion \geq 10 ELISA Ab units	Post-dose	N = 370 353 (95%) [93 – 97]	N = 515 500 (97%) [95 – 98]	-2% [-4.5 – 0.8]
		N = 337 325 (96%) [94 – 98]	N = 459 448 (98%) [96 – 99]	-1% [-3.9 – 1.2]
Rubella seroconversion \geq 10 IU/mL	Post-dose	N = 337 333 (99%) [97 – 100]	N = 459 456 (99%) [98 – 100]	-1% [-2.4 – 0.8]
		N = 337 333 (99%) [97 – 100]	N = 459 456 (99%) [98 – 100]	-1% [-2.4 – 0.8]

* Proportion of subjects in MenACWY + MMRV group receiving MMR and V was approximately 16%, while proportion receiving MMRV was approximately 84%. Proportion of subjects in MMRV group receiving MMR and V was approximately 29%, while proportion receiving MMRV was approximately 71%

Similarly the analyses of GMTs were fully supportive of non-inferior immunogenicity for the MMRV vaccine antigens when administered with or without Menveo.

Clinical safety

Study V59P23 was a pivotal safety study in infants who received 4 dose (2, 4, 6, 12 months of age) Menveo vaccinations. Immunogenicity data were not collected in this study. The design of this study was as follows:

Table 15: Study V59P23 (safety study of 4 dose schedule in infants)

Objectives of the Study	Study Design and Type of Control	Subjects' Ages at Enrolment; Geographic Location	Study Group	Test Products		Number of Subjects Enrolled
				MenACWY Vaccination Schedule (Months of Age)	Routine Vaccination Schedule (Months of Age)	
V59P23						
Assessment of safety/tolerability: percentage of subjects with at least one severe systemic reaction 7 days postvaccination (MenACWY+R vs. Routine)	Randomized, open-label, parallel group, multicenter	2 months US, Taiwan, Costa Rica, Guatemala, Peru, Panama	MenACWY+Routine vaccines (MenACWY+R)	2, 4, 6, 12	2, 4, 6, 12	5772
			Routine vaccine only (Routine)	None	2, 4, 6, 12	1972

Overall, in the US trial population, with the 4 dose infant vaccination in studies V59P14, V59_33 and V59_P23, solicited adverse events (AEs) were reported in 55% versus 68% subjects in Menveo and Control (routine infant vaccination) groups respectively, whereas unsolicited AEs were reported in 44% versus 48% subjects in Menveo and Control groups respectively.

Overall, in the non-US trial population, with the 4 dose infant vaccination in studies V59P14, V59_33 and V59_P23, solicited AEs were reported in 45% versus 32% subjects, and unsolicited AEs were reported in 56% versus 52% subjects in Menveo and Control groups respectively:

Table 16: Summary of 4 dose MenACWY subjects with safety data from Studies V59P14, V59P23 and V59_33 trials

	Total 4-Dose MenACWY Safety Population	Solicited AEs through the 4 th Dose		Unsolicited AEs through 1 Month Post- 4 th Dose	
		Number of subjects with reported solicited AEs	Number of controlled ^a subjects with reported solicited AEs	Number of subjects with reported unsolicited AEs	Number of controlled ^a subjects with reported unsolicited AEs
V59P14 – US	995	810	690	820	690
V59P14 – LA	1725	1554	825	1555	825
V59P23 – Detailed, US	1403	1102	1102	1185	1185
V59P23 – Non-detailed, US	1440	0	0	1197	1197
V59P23 – Non-detailed, Non-US	2917	0	0	2746	2746
V59_33 – US	255	0	0	213	213
TOTAL	8735	3466	2617	7716	6856
Total US (% Total)	4093 (47%)	1912 (55%)	1792 (68%)	3415 (44%)	3285 (48%)
Total Non-US (% Total)	4642 (53%)	1554 (45%)	825 (32%)	4301 (56%)	3571 (52%)

^a Contemporaneously enrolled, controlled subjects; based on the number of control subjects in the groups created by the timing of Amendments 4 and 5 to study V59P14 and a 2:1 randomization ratio for the MenACWY-control group.

As noted, V59P23 was a dedicated safety study and had a predefined primary safety hypothesis in respect of solicited adverse reactions (ADRs) which was not met as follows:

Table 17: Results of V59P23 Primary safety outcome

Systemic Reaction	Number (%), 95% CI of Subjects with Solicited Reaction		ACWY-D minus RVAX-D Vaccine Group Difference, 95% CI ^a	Primary Safety Objective Criterion
	ACWY-D N=1330	RVAX-D N=456		Upper 95% CI limit <6%
Severe	197 (15%)	54 (12%)	3.0% (-0.7, 6.3)	Not met

In an analysis using a restricted safety set (RSS), the criterion was met:

Table 18: Results of V59P23 Primary safety outcome in RSS

Systemic Reaction	Number (%), 95% CI of Subjects with Solicited Reaction		ACWY-D minus RVAX-D Vaccine Group Difference, 95% CI ^a	Primary Safety Objective Criterion
	ACWY-D N=1181	RVAX-D N=405		Upper 95% CI limit <6%
Severe	140 (12%)	41 (10%)	1.7% (-1.9, 4.9)	Met

Across all studies, 14 serious adverse events were considered by the investigator to be possibly related to Menveo, of which 12 occurred in subjects who received the final formulation of Menveo concomitantly with routine childhood vaccines:

Table 19: Serious adverse reactions considered possibly related to vaccination by the investigator. [Patient identifier column has been redacted from this table]

SAE	Most recent vaccination
Febrile Convulsion	8 days after 4 th dose
Febrile Convulsion	7 days after 4 th dose
Febrile Convulsion	3 days after 4 th dose
Febrile Convulsion	38 days after 3 rd dose
Pyrexia	1 day after 1 st dose
Complex Partial Seizure	31 days after 2 nd dose
Epilepsy	17 days after 3 rd dose
ADEM*	35 days after 4 th dose
Kawasaki Disease	29 days after 3 rd dose
Kawasaki Disease	20 days after 1 st dose
Kawasaki Disease	12 days after 1 st dose
Groin Abscess	83 days after 3 rd dose

*Acute Disseminated Encephalomyelitis.

Note the 3 cases of Kawasaki Disease considered possibly-related to the vaccination were out of a total of 7 reported potential cases (1 case in control group) as follows:

Table 20: Possible cases of Kawasaki disease in MenACWY studies

Case #	1	2	3	4	5	6	7
Trial	V59P23	V59P23	V59P14	V59P23	V59P23	V59P23	V59P7
Gender	Female	Male	Male	Female	Female	Male	Female
Study group	Control	MenACWY	MenACWY	MenACWY	MenACWY	MenACWY	MenACWY
Onset latency from vaccination	87 days post-3 rd dose	12 days post-1 st dose	29 days post-3 rd dose	25 days post-1 st dose	98 days post-3 rd dose	149 post-3 rd dose	148 post-2 nd dose
Related to study vaccine? ^a	No	Possibly	Possibly	Possibly	No	No	No
Adjudication Committee outcome	Possible Incomplete KD	Possible KD	Incomplete KD	Possible Incomplete KD	Possible KD	Possible KD	Not consistent with KD

^a Assessment by study PI or sponsor.

The sponsor reports that based on 5 confirmed cases of Kawasaki Disease (KD) with a cumulative 15,776 person-years (PY) of surveillance in all MENVO studies *in children up to the age of 5 years*, the estimated annual incidence of KD is 32 per 100,000 children (95%CI 10, 74). The estimated annual incidence of KD in control group based on 1 case and 4,722 patient years (PY) is 21 cases per 100,000 children (95%CI 0.5, 118). This amounts to a relative risk (RR) of developing KD of 1.5 fold (95%CI 0.17, 70) with Menveo vaccination.

A total of 11 deaths were reported (all were in 2 studies that is, V59P23 and V59P14). Of these 8 were reported in the Study V59P23 (one in Control, 7 in Menveo group) and 3 in the Study V59P14 as follows:

Table 21: Details of deaths [patient identifiers have been redacted from table]

Cause of Death	Most recent vaccination prior to death/Comment
Sudden death	(b)(6) days after 1 st dose
	Found unresponsive; h/o GERD; Autopsy: pulmonary edema and pneumonitis
Septic shock	(b)(6) days after 1 st dose
Head injury	(b)(6) days after last dose
Bronchopneumonia	(b)(6) days after 2 nd dose
Lung infection	(b)(6) days after 3 rd dose
Cardiorespiratory Failure	(b)(6) days after 1 st dose
	(b)(6) days after 1 st dose: four day hospitalization for bilateral pneumonia
Respiratory failure	(b)(6) days after 1 st dose
Cardiac Arrest	(b)(6) days after last dose
Auto accident	(b)(6) days after 4 th dose
Sepsis	(b)(6) days after 2 nd dose
	Tetralogy of Fallot diagnosed 21 days after 2 nd dose
TAPVC with Pul. HTN*	(b)(6) days after 1 st dose
	(b)(6) days after 1 st dose: TAPVC diagnosed, then subject withdrawn

*Total Anomalous Pulmonary Venous Connection with Pulmonary Hypertension

Post-market data/Risk management plan (RMP)

Please see the RMP evaluation above.

Please also see review of 4 post-market studies (V59_36, V59_57, V59_340B and V59_540B) in the CER (Attachment 2), in particular the Study V59_40B which was a large (N=55,397) surveillance study in 11 to 21 year old population of past ACWY recipients.

The information on coadministration of 13 valent pneumococcal conjugate vaccine in Study V59_36 is noted.

Also noted is a potential association with Bell's palsy in Study P59_340B on co-administration with routine infant vaccines. The study found an increased relative risk of 2.9 fold (95%CI 1.1, 7.5) for Bell's palsy in 84 days (risk window) following Menveo vaccination mainly on co-administration with other vaccines.

The clinical evaluator has also drawn attention to a case of GBS reported in the FDA approved prescribing information. The sponsor has indicated that this may have occurred in relation to polysaccharide vaccine licensed in Canada and the US. The sponsor has been requested to clarify the nature of Menactra vaccine used as active comparator in the Study V59P20.

The sponsor is also requested to comment whether vaccine (efficacy) failure data specific to completed 4 dose series and 2 dose catch-up series in infants and one dose vaccination in 2 to 10 years old children are available from post-market surveillance and include a summary in its response to this overview if available.

Risk-benefit analysis

Delegate's considerations

1. The prophylactic efficacy of meningococcal vaccines cannot be established in prospective clinical trials as the incidence of disease is extremely low. The use of immunogenicity data (serum bactericidal activity with human complement) is well established and acceptable for regulatory purposes. This is expected to be supplemented with appropriate post-market surveillance.
2. In Studies V59P14 and V59_33, the predefined criterion (*percentage of subjects with hSBA \geq 1:8*) with a 4 dose infant schedule (at 2, 4, 6 and 12-16 months of age) were met for all 4 serogroups (ACWY) in both studies:
 - LL95%CI were 83%, 90%, 93% and 92% for A, C, W, Y serotypes respectively in V59_33.
 - LL95%CI were 87%, 92%, 96% and 96% for A, C, W, Y serotypes respectively in V59P14 (US cohort).
 - LL95%CI were 89%, 94%, 97% and 95% for A, C, W, Y serotypes respectively in V59P14 (LA cohort).

The Study V59_33 is the largest single study providing pivotal immunogenicity data for the 4 dose series in infants and overtakes the previous study V50P14 in terms of design, follow-up and reliability of data, although the recommendation for the 4th dose in 12-16 months age range is based on the LA cohort in the Study V59P14.

A 3-dose infant series (2, 4, 6 months) is not supported by either study (V59_33 or V50P14). There was a significant decline in the *percentage of children with hSBA \geq 1:8* at pre Dose-4 time-point in studies V59_33 and V59P14 (US cohort) that is antibody persistence at 6 months (2, 4, 6, 12 months schedule) and at pre Dose-4 time-point in

Study V59P14 (LA cohort) that is, antibody persistence at 10 months (2, 4, 6, 16 months schedule).

- Pre Dose-4 LL95%CI were 4%, 30%, 62% and 45% for A, C, W, Y serotypes respectively in Study V59_33.
- Pre-Dose-4 LL95%CI were 4%, 39%, 60% and 49% for A, C, W, Y serotypes respectively in Study V59P14 (US cohort).
- Pre Dose-4 LL95%CI were 8%, 15%, 52% and 37% for A, C, W, Y serotypes respectively in Study V59P14 (LA cohort).

It is noted that long-term antibody persistence data for the 4 dose schedule are currently not available. The sponsor is requested to comment and provide a summary of antibody persistence data, if available, from the cohorts of subjects who completed 4 dose vaccination schedules in these 2 trials.

3. The *percentage of subjects with hSBA \geq 1:8* criterion was similarly satisfactorily met with a 2 dose catch-up schedule in 7-23 months old unvaccinated infants in Study V59P21 (Dose 1 at 7 months of age and Dose 2 in 2nd year of life). The LL95%CI was 84%, 98%, 96% and 93% in A, C, W and Y serotypes respectively.

In its pre-ACV response, the sponsor is requested to comment and provide summary of longer term antibody persistence data from this study if available.

4. There was some evidence of immune interference (seroresponse) in respect of 7-valent pneumococcal conjugate vaccine (individual antigens 6B and 23F but not the overall response in terms of 0.35 μ g/mL level) and pertussis in the 4 dose infant series. The results were more in line with the predefined non-inferiority criteria based on GMTs.
5. In children 2 to 10 years of age, a single dose Menveo was non-inferior to a single dose of Menactra overall with respect to percentages of subjects with hSBA \geq 1:8, but non-inferiority could not be demonstrated for serotype A in the 2-5 years old and the 6-10 old age strata separately. The results for serotypes C, W and Y were equivalent or better, although a 2nd dose of Menveo 2 months later in Menveo group resulted in a much stronger immune response.

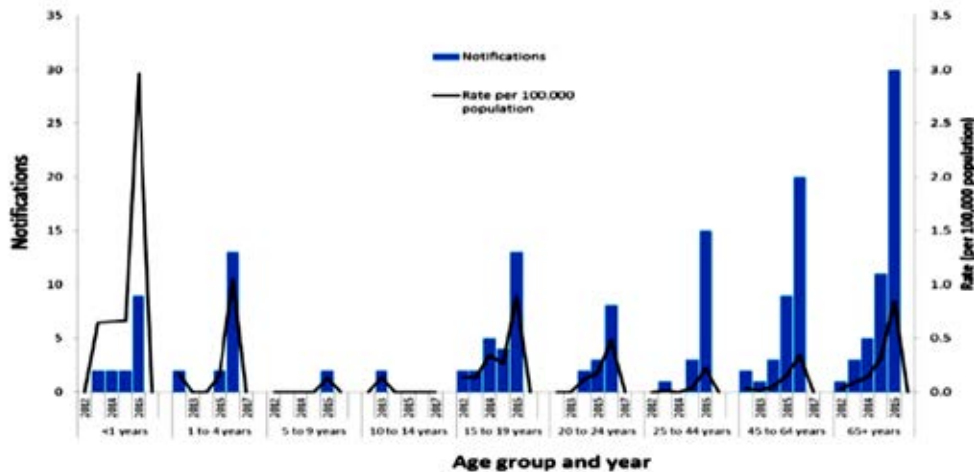
The sponsor has been requested to clarify the type of Menactra formulation (polysaccharide or conjugate) that was used in this study. Longer term persistence data (5 years) following one dose (Study V59P20E1) is proposed for inclusion in the Australian PI, which reports that percentages of subjects with hSBA \geq 1:8 was 32% and 56% against serogroup C, 74% and 80% against serogroup W and 48% and 53% against serogroup Y in age groups 2-5 years and 6-10 years respectively. For serogroup A, 14% and 22% of subjects in 2-5 and 6-10 years of age groups respectively had hSBA \geq 1:8. The sponsor is requested to include of a summary of long-term persistence data from this study in its Pre-ACV response by primary doses (1 or 2) and by booster where relevant.

6. In terms of safety, specifically with respect to the 4 dose series proposed in infants, attention of the ACV is brought to the reported imbalance in incidence of deaths, Kawasaki Disease and Bell's palsy in association with Menveo and routine infant/toddler vaccines. A small degree of immune response interference, of undefined significance, for the latter vaccines (pneumococcal/pertussis) was also noted.

None of the deaths were considered causally-related to the study vaccines. However, causality is not an issue in the presence of controlled data and any imbalance in deaths (and other serious outcomes) in vaccine trials in healthy infants require further explanation.

The Delegate does note different exposures in the two groups (nearly 3 times more follow up in Menveo groups than for control groups). Absence of deaths in the Study V59_33 is also noted. The burden of disease in <1 years of age group is also acknowledged:

Figure 1: Age specific notifications and rate MenW notifications Australia 2012-2017 YTD



*Data extracted from the National Notifiable Diseases Surveillance System on 9 January 2017.

(Department of Health, Invasive Meningococcal Disease National Surveillance Report)

Summary of issues

- Risk/Benefit of 4 dose infant schedule.
- Adequacy of single dose schedule in 2 to 10 years of age group.

Proposed action

The data support the use of 2 dose Menveo vaccination schedule in infants (Dose 1 at 7 months of age, Dose 2 in 2nd year of life). This may be considered a primary or alternative ACWY vaccination strategy in infants rather than a catch-up schedule in unvaccinated infants.

Request for ACV advice

The ACV is requested to provide advice on the following specific issues:

1. Advice is requested from the ACV regarding Risk/Benefit of the proposed 4 dose infant schedule (2, 4, 6 and 12-16 months of age).
2. Advice is requested from the ACV of the suitability of a 2 dose schedule based on the 2 dose data in the Study V59V20.

The Committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

This Overview was submitted for advice from the ACV.

Response from Sponsor

Executive Summary

In consultation with the Office of Health Protection in the Commonwealth Department of Health and in light of the current public health environment surrounding meningococcal

disease, GSK is applying for registration of Menveo for use in infants 2 months old and over and children 2 to 10 years. GSK and the TGA have cooperated to bring this application before the ACV in an expedited timeframe.

- According to the Invasive Meningococcal Disease National Surveillance Report published in 2017³, serogroup W followed by B are now the most common cause of invasive meningococcal disease in Australia. There are currently conjugated MenACWY vaccines registered for use in children 2 years and above, however, none are registered for use in infants who are at the greatest risk of invasive meningococcal disease, with a notification rate up to 10 times higher than the national average.⁴
- A recognised Australian expert in paediatric meningococcal disease supports the medical need for vaccination of infants and children against meningococcal serotypes ACWY and hence supports GSK's application.

GSK supports the clinical evaluator's recommendation to register Menveo for use in infants and children. GSK also welcomes the Delegate's preliminary assessment that the 2 dose Menveo vaccination schedule at 7 months and 12 months of age is supported, and acknowledges the advice being sought on GSK's proposed 4 dose primary schedule in infants from 2 to 6 months of age and single dose schedule in children 2 -10 years of age.

GSK's application aligns with the registered use of Menveo in the US (since 2013), Canada (since 2014), Singapore (since 2014) and many other countries worldwide.

Pivotal Clinical Studies in infants 2 months – 23 months

- Supports a 4 dose vaccination schedule in infants with the primary 3-dose series at 2, 4 and 6 months demonstrating a robust immune response against all 4 serogroups 1 month after the third vaccination.
- The fourth dose of Menveo given at 12 or 16 months of age induced a robust increase in antibody titres to a greater degree than seen after the primary vaccination series.
- The clinical studies also support a catch up 2 dose series for infants not vaccinated in the first six months of life.
- Optimum protection in the first year of life is not provided by the 2 dose schedule (see GSK position below)
- The sponsor believes that registration of both the primary 4 doses and catch up 2 dose schedules for infants provide immunisation flexibility for the prescribing physician.

Pivotal Studies in children 2 to 10 years of age

- Demonstrates non inferiority to Menactra (registered in Australia for use in this age cohort).
- Demonstrates substantial antibody persistence up to 5 years in the open labelled extension study.
- A single dose schedule in line with the registered dose in children over 11 years of age is justified.

³ Department of Health. Invasive Meningococcal Disease National Surveillance Report: with a focus on MenW. 9 January 2017.

[http://www.health.gov.au/internet/main/publishing.nsf/Content/5FEABC4B495BDEC1CA25807D001327FA/\\$File/Surveillance-report-Jan2017.pdf](http://www.health.gov.au/internet/main/publishing.nsf/Content/5FEABC4B495BDEC1CA25807D001327FA/$File/Surveillance-report-Jan2017.pdf) (Accessed May 2017)

⁴ Calculated using data extracted from the National Notifiable diseases surveillance system (NNDSS) <http://www9.health.gov.au/cda/source/cda-index.cfm> and the Australian Bureau of Statistics (ABS) Birth data

<http://www.abs.gov.au/ausstats/abs@.nsf/Latestproducts/3301.0Main%20Features32015?opendocument&ntabname=Summary&prodno=3301.0&issue=2015&num=&view> (Accessed May 2017)

Safety Profile in infants and children

The safety profile of Menveo with all proposed dosing schedules in infants and children is acceptable as concluded in the benefit risk assessment of the clinical evaluation report where the evaluator states '*the vaccine has been shown to be well tolerated with acceptable local and systemic reactogenicity*'.

Conclusion

The benefit-risk balance is favourable, as assessed by the TGA clinical evaluator and supported by a recognised Australian clinical expert, for registration of the 4 dose and 2 dose catch up schedules in infants 2 months of age and over and a single dose schedule in children 2 to 10 years of age.

Specific Questions Raised by the TGA Delegate for the ACV's advice***Risk Benefit of the proposed 4 dose infant schedule (2, 4, 6 and 12-16 months)***

GSK consider a 4 dose vaccination schedule given at 2, 4, 6 and 12 months of age, is the appropriate schedule for priming of infants based on the clinical data available.

The sponsor has developed Menveo as a 4 dose vaccine in infants starting vaccination from 2 months of age, with the first 3 doses given at 2, 4 and 6 months of age, and a fourth dose administered in the second year of life. Substantial immunogenicity and safety data was generated in clinical studies V59P14, V59_33 and V59_36 to support this vaccination schedule. Across these studies, a 3-dose series in the first year of life resulted in a robust immune response against all 4 serogroups, by 1 month after the third vaccination (with percentages of subjects with hSBA titres $\geq 1:8$ ranging from 67%-89% against serogroup A, 95%-97% against serogroup C, 96%-99% against serogroup W and 91%-98% against serogroup Y). The fourth dose of Menveo given at 12 or 16 months of age induced a robust increase in antibody titres to a greater degree than seen after the primary vaccination series (overall, 89% to 100% of subjects had hSBA titres $\geq 1:8$ after the 4th dose) (Table 22). Furthermore, there was no impact of repeated doses either on reactogenicity or on the overall safety profile of the subjects.

Table 22: Percentages of infants with hSBA \geq 1:8 and hSBA GMTs: Post infant series, pre toddler dose and post toddler dose

	V59P14				V59_33		V59_36	
	US Cohort		LA Cohort ¹		% hSBA \geq 1:8	GMTs	% subjects with hSBA \geq 1:8	GMTs
	% hSBA \geq 1:8	GMTs	% hSBA \geq 1:8	GMTs				
MenA	N=212		N=268		N=168		N=157	
1 month post 3 rd dose	67% (61-74)	13 (11-16)	89% (85-93)	43 (36-52)	76% (69-82) N=159	22 (17-27) N=159	84% (77%-89%)	28 (23-35)
1 month post 4 th dose	94% (87-98) N=84	77 (55-109) N=84	95% (89-98) N=120	146 (113-188) N=120	89% (83-93)	54 (44-67)	96% (91%-98%) N=141	59 (45-77) N=141
MenC	N=204		N=272		N=156		N=176	
1 month post 3 rd dose	97% (93-99)	108 (92-127)	97% (94-99)	150 (127-177)	96% (91-98) N=145	83 (66-105) N=145	95% (91%-98%)	86 (70-104)
1 month post 4 th dose	98% (92-100) N=86	227 (155-332) N=86	98% (94-100) N=122	283 (225-355) N=122	148 (95%) (90-98)	135 (107-171)	99% (95%-100%) N=152	124 (99-156) N=152
MenW	N=197		N=264		N=153		N=162	
1 month post 3 rd dose	96% (93-99)	100 (86-116)	98% (96-100)	182 (159-208)	97% (93-99) N=139	74 (60-91) N=139	99% (96%-100%)	90 (77-104)
1 month post 4 th dose	100% (96-100) N=85	416 (288-602) N=85	100% (97-100) N=112	727 (586-903) N=112	97% (93-99)	215 (167-277)	99% (96%-100%) N=138	248 (202-303) N=138
MenY	N=182		N=263		N=153		N=163	
1 month post 3 rd dose	96% (92-98)	73 (62-86)	98% (96-99)	125 (107-146)	91% (85-95) N=135	48 (39-59) N=135	94% (90%-97%)	52 (43-64)
1 month post 4 th dose	100% (96-100) N=84	395 (269-580) N=84	99% (95-100) N=109	590 (463-751) N=109	96% (92-99)	185 (148-233)	99% (96%-100%) N=146	212 (175-258) N=146

Source: V59P14 CSR 10 MAR 11; V59_33 CSR 09 OCT 12; V59_36 CSR 01 AUG 2015.

Data from these studies also show that Menveo can be co-administered with several other routine infant vaccines, without compromising the immune response or the safety profile of any vaccine administered. There was a small degree of immune interference noted for some of the pertussis antigens included in the routinely administered vaccine, as well as up to 2 (out of 13) pneumococcal vaccine serotypes across studies, only after completion of the 3 infant doses, while no interference was seen after the fourth dose. Of note, no single antigen failed the non-inferiority assessment consistently in every study and there were also substantial percentages of subjects with antibody levels above pre-specified protective thresholds for all antigens, suggesting that these are chance findings that inevitably arise in the setting of multiple comparisons.⁵ The clinical evaluation report recommends '*licencing of the vaccine for use in infants means that it can be given in conjunction with other infant vaccines given at the same time points*'.

While an alternative 2 dose vaccination schedule starting at 6 to 8 months of age with a second dose at 12 months of age has also been explored (in Studies V59P21, V59P22 and V59P14), this schedule does not provide optimal protection to infants before the administration of the second dose at 12 months of age. Indeed, antibody titres after one dose of Menveo given at 6 to 8 months of age are low, specifically for serogroups W and Y, with only 31% to 43% and 32% to 37% of subjects, respectively, achieving hSBA titres \geq 1:8, compared with 91% to 99% of subjects after 3 infant doses. Against serogroup A as

⁵ Gasparini et al. Safety and Immunogenicity of a Quadrivalent Meningococcal Conjugate Vaccine and Commonly Administered Vaccines After Coadministration. *Pediatr Infect Dis J.* 2016;35:81-93)

well, protection offered by a single dose is lower, with only 42% to 50% of subjects achieving hSBA titres $\geq 1:8$, compared with 67% to 89% of subjects after 3 infant doses. The hSBA GMTs after a single dose at 6 to 8 months are also substantially lower (6.8 to 8.16 against serogroup A, 26 to 32 against serogroup C, 5.11 to 5.75 against serogroup W and 4.09 to 4.82 against serogroup Y) than those seen after 3 primary doses at 2, 4 and 6 months (GMTs ranging from 13 to 43 against serogroup A, 83 to 150 against serogroup C, 74 to 182 against serogroup W and 48 to 125 against serogroup Y). It is also noteworthy that, although the levels of seroprotection achieved after completion of a 4 dose primary or a 2 dose series are comparable, hSBA GMTs after completion of the 2 dose series (37 to 68 against serogroup A, 180 to 224 against serogroup C, 119 to 191 against serogroup W and 88 to 137 against serogroup Y) are lower than those seen after completion of the 4 dose infant series (Table 23), against serogroups A, W and Y, and are similar against serogroup C.

Table 23: Percentages of infants with hSBA $\geq 1:8$ and hSBA GMTs in Study V59P21

Serogroup	% hSBA $\geq 1:8$	GMTs
Men A	N=379	N=379
Post-first dose (8-10 months of age)	175 (50%) (45-56)	8.16 (6.96-9.58)
	N=349	N=349
Post-second dose (13 months of age)	334 (88%) (84-91)	37 (32-42)
Men C	N=199	N=199
Post-first dose (8-10 months of age)	175 (88%) (83-92)	26 (22-31)
Post-second dose (13 months of age)	195 (100%) (98-100)	180 (158-205)
	N=195	N=195
Men W	N=199	N=199
Post-first dose (8-10 months of age)	73 (37%) (30-44)	5.11 (4.15-6.29)
Post-second dose (13 months of age)	193 (98%) (96-100)	119 (101-139)
	N=196	N=196
Men Y	N=198	N=198
Post-first dose (8-10 months of age)	60 (31%) (24-38)	4.09 (3.36-4.98)
	N=196	N=196
Post-second dose (13 months of age)	191 (96%) (93-99)	88 (73-105)

Therefore, based on the immunogenicity data a 3 dose series in infants offers better protection during the first year of life, when the risk for acquiring meningococcal disease is the highest. Infants less than one year are at the greatest risk of invasive meningococcal disease, with a notification rate up to 10 times higher than the national average.⁴ Infants less than one year also have the highest rate of hospitalisation and death due to meningococcal disease.⁶ As such, it is critical to afford the maximum possible protection for infants during this high risk period, as early as possible.

The safety profile of Menveo is supported via exposure of 31,866 participants in clinical trials and recipients of 28,399,909 doses worldwide. The rise in antibody titres following the fourth dose in the second year of life demonstrates the additional benefit that this dosing regimen can provide to a vulnerable population, in the absence of greater safety concerns. GSK believes that the available clinical data for Menveo demonstrate clearly that

⁶Dey, A. Et al. Summary of National Surveillance Data on Vaccine Preventable Diseases in Australia, 2008-2011. Communicable Diseases Intelligence. 2016; 40(Supplement).

the benefits of protection against the serotypes ACWY outweigh the risks of vaccination, which in turn, are greatly outweighed by the risks of non-vaccination.

Based on these considerations, GSK continues to consider a 4 dose vaccination schedule given at 2, 4 and 6 months of age, and a fourth dose administered in the second year of life, as the primary schedule for priming of infants, a population that remains at the highest risk for contracting invasive meningococcal disease. In addition, the 2 dose schedule at 7 and 12 months of age, also supported by the data available ensures an appropriate catch up schedule is available for those infants not vaccinated within the first 6 months of life.

Suitability of a 1 or 2 dose schedule in children 2 to 10 years of age

GSK considers that a single dose of Menveo provides adequate protection for children aged 2 through 10 years and is supported by the efficacy and safety data available.

Menveo is recommended for use as a single dose in children 2 to 10 years of age in the majority of the countries in which this product is registered for use in children 2 years and over. The clinical data supporting this recommendation comes from the pivotal V59P20 trial conducted in the US, in which 1170 children were vaccinated with Menveo and 1161 received the comparator vaccine (Menactra) in the per protocol populations. A single dose of Menveo induced robust immune responses, with 72% to 90% of subjects achieving hSBA titres $\geq 1:8$ at 1 month after vaccination and seroresponse rates ranging from 62% to 72%, across serogroups. In the same study, a separate group of children, 2 through 5 years of age (N=297) in the per protocol population were immunized with two doses of Menveo, two months apart, with 91% to 99% of subjects achieving hSBA titres $\geq 1:8$ at 1 month after vaccination and seroresponse rates ranging from 89% to 98%, across serogroups.

Based on these results in a limited pool of children aged 2-5 years, the sponsor decided to explore the potential benefit of a second dose in children 2 to 10 years of age in another study also conducted in the US, V59_57.⁷ This study compared the immunogenicity, safety and 1 year antibody persistence of a single-dose and a 2 dose series of Menveo in children aged 2 to 5 years and 6 to 10 years. A serial gatekeeping procedure was used to assess superiority of a 2 dose schedule in these age cohorts.

In this study, both a single dose and a 2 dose series of Menveo were found to be immunogenic, eliciting protective antibody responses in the majority of 2 to 10 year-old children. At one month postvaccination, hSBA seroresponse rates, percentages of subjects with hSBA $\geq 1:8$, and hSBA GMTs were higher in the 2 dose group than in the 1 dose group against serogroups A, C and Y. The differences in antibody responses between the 2 dose and 1 dose groups were larger in the 2 through 5 years of age cohort than in the 6 through 10 years of age cohort, which could be explained by the relative immaturity of the immune system and the lower likelihood of natural immunity in the younger cohort. However, statistical superiority of a 2 dose schedule could only be demonstrated for serogroups C and Y in 2 to 5 year old children and for serogroup Y in 6-10 year old children. Furthermore, antibody persistence at 1 year after vaccination was also assessed in this study and antibody titres declined in both age cohorts and dose groups over 12 months. While subjects in the 2 dose group still had higher antibody titres than those in 1 dose group by 12 months after vaccination, the difference between groups was less pronounced at 1 year post-vaccination than at 1 month post-vaccination, especially among older children. Of note, in another study assessing antibody persistence at 5 years after a 1 or 2 dose series in 2 5 year olds (V59P20E1)⁸, there was no appreciable difference in antibody

⁷ Johnston et al. Comparative Assessment of a Single Dose and a 2 dose Vaccination Series of a Quadrivalent Meningococcal CRM-conjugate Vaccine (MenACWY-CRM) in Children 2 to 10 Years of Age. *Pediatr Infect Dis J*. 2016 Jan;35(1):e19-27

⁸Block et al. Antibody persistence 5 years after vaccination at 2 to 10 years of age with Quadrivalent MenACWY-CRM conjugate vaccine, and responses to a booster vaccination. *Vaccine*. 33 (2015) 2175–2182

persistence between subjects who received 2 doses or 1 dose of Menveo while both groups of subjects responded equally well to a booster dose given 5 years after primary vaccination series.

Based on the above results, the sponsor contends that a single dose of Menveo provides adequate protection for children aged 2 through 10 years. The value of administration of an additional dose in children aged 6 to 10 years is debatable. While an additional dose could potentially provide an immediate benefit for those children aged 2 to 5 years at higher risk for invasive meningococcal disease (for example, those with an immunocompromised status or living in an endemic area), routine administration of 2 doses of MenACWY is not warranted as 2 doses are not associated with greater lasting protection compared with a single dose.

Other issues raised by the TGA Delegate

1. *The sponsor is requested to please confirm whether Menactra used in this study (V59P20) was a conjugate or a polysaccharide formulation.*

Menactra, as used in Study V59P20, is a vaccine containing polysaccharides of meningococcus types A, C, W and Y, conjugated to diphtheria toxoid.

2. *The sponsor is also requested to comment whether vaccine (efficacy) failure data specific to completed 4 dose series and 2 dose catch-up series in infants and one dose vaccination in 2 to 10 years old children are available from post-market surveillance and include a summary in its Pre-ACV response if available.*

Since launch, GSK has received 41 cases suggestive of Menveo vaccination failure. Of these, 18 were cases of clinical vaccination failure (that is, cases that describe the occurrence of the specific vaccine-preventable disease in a person who is appropriately and fully vaccinated, taking into account the incubation period and the normal delay for the protection to be acquired as a result of immunisation). All of these 18 cases were concerning adult vaccinees. GSK does not have sufficient post-marketing data to make a conclusion on vaccine efficacy in the dosing regimens or age groups referred to.

3. *It is noted that long-term antibody persistence data for the 4 dose schedule are currently not available. The sponsor is requested to comment and provide a summary of antibody persistence data, if available, from the cohorts of subjects who completed 4 dose vaccination schedule in these 2 trials (V59P_14 and V59_33)*

Antibody persistence after 4 infant doses of Menveo was assessed in Study V59P14E1, which was a Phase IIIb, multicentre, open-label, controlled extension of the V59P14 trial.⁹ This extension was conducted at US sites with adequate enrolment that participated in the parent study, and enrolled subjects who received either 4 primary doses (at 2, 4, 6, and 12 or 13 months of age) and those who received 2 doses of Menveo in the second year of life. Antibody persistence data was assessed at 40 and 60 months of age.⁹ In subjects who received 4 primary doses, antibody levels declined substantially for serogroups A and C by 40 months of age, 27 to 28 months after the fourth dose, with percentages of subjects with hSBA titres \geq 1:8 ranging from 7%-16% for serogroup A and 27%-32% for serogroup C. Levels of bactericidal antibodies against serogroups W (68% to 70% subjects with hSBA titres \geq 1:8) and Y (53% to 60% subjects with hSBA titres \geq 1:8) also declined although to a lesser degree. By 60 months of age, 47 to 48 months after last infant dose, antibody titres declined further across serogroups but the magnitude of the decline was less pronounced. Of note, at both time points, antibody titres in vaccinated subjects were higher than those seen in age-matched naïve controls.

⁹ Baxter et al. Persistence of the immune response after MenACWY-CRM vaccination and response to a booster dose, in adolescents, children and infants. Human Vaccines and Immunotherapeutics. 2016, VOL. 12, NO. 5, 1300-1310

Antibody persistence was not evaluated for subjects from Study V59_33.

4. *In its pre-ACV response, the sponsor is requested to comment and provide a summary of longer term antibody persistence data from this study (v59_P21) if available.*

Antibody persistence was not evaluated for subjects from Study V59P21.

5. *The sponsor is requested to include a summary of long-term persistence data from this study (V59_P20E1) in its Pre-ACV response by primary doses (1 or 2) and by booster where relevant.*

Antibody persistence at 5 years after primary vaccination was assessed in Study V59P20E1⁸, a Phase IV open-label controlled extension of the V59P20 study. There was substantial antibody persistence observed against serogroups C, W and Y, with the percentages of subjects with hSBA titres ≥ 8 being 32% and 56% against serogroup C in subjects 2 to 5 and 6 to 10 years of age, respectively, 74% and 80% against serogroup W, and 48% and 53% against serogroup Y. For serogroup A, the decline in circulating bactericidal antibody titres were greater, with 14% and 22% of subjects 2 to 5 and 6 to 10 years of age, respectively, retaining hSBA titres ≥ 8 . Levels for all 4 serogroups were higher than those seen in meningococcal vaccine-naïve children of similar ages. In the parent Study V59P20, higher antibody responses were seen in 2 to 5 year old children after two doses of Menveo than in those who only received one dose. However, this difference did not persist 5 years later, as levels of residual antibodies were similar in both groups of children, now aged 7 to 10 years.

Children in this extension study were also revaccinated with a single dose of Menveo 5 years after priming. After a booster dose, the fold increases in hSBA GMTs were characteristic of booster responses. The magnitude of antibody GMTs and ratio of GMTs post to pre vaccination were significantly higher in previously vaccinated subjects than in age matched vaccine naïve controls. All children revaccinated at 5 years had hSBA titres ≥ 8 against each of the four serogroups, except one subject who did not respond to serogroup A. Responses to the booster vaccination were similar regardless of the number of previous doses in younger children, or the age group when the primary vaccinations were administered.

6. *Attention of the ACV is brought to the reported imbalance in incidence of deaths, Kawasaki Disease and Bell's palsy in association with Menveo and routine infant/toddler vaccines. None of the deaths were considered causally related to the study vaccines. However, causality is not an issue in the presence of controlled data and any imbalance in deaths (and other serious outcomes) in vaccine trials in healthy infants require further explanation.*

GSK agrees that assessment of a causal relationship between an event and a vaccine requires inclusion of all cases of that event, not solely those considered by the reporter or investigator as related to the vaccine. However, a numerical or statistical imbalance alone is insufficient evidence of a causal association. Analysis of each of the deaths occurring in Studies V59P20 and V59P14 did not find a safety concern. Of the 8 deaths in the groups receiving Menveo, 6 occurred more than 31 days after vaccination. The other 2 deaths were due to sepsis and pneumonitis, for which there is little biological plausibility for a causal association with vaccine.

Analysis of each of the cases of Kawasaki's disease (KD) received in studies V59P7, V59P23 and V59P14 did not find sufficient evidence of a causal association. In the groups receiving Menveo, 3 of the 6 cases of KD occurred beyond the 6-week risk period. Statistical analysis of these cases found a relative risk of 1.5, however the confidence interval included 1, therefore it is possible that there is no correlation between the vaccinated group and KD. Since launch, GSK is aware of 10 such cases.

The imbalance in the incidence of Bell's palsy in Study V59_340B led GSK to include facial paresis in the Global Product Information. However, the EMA concluded that the evidence was not sufficient to warrant inclusion of this event in the EU Summary of Product Characteristics (SmPC) and rejected the change; therefore, facial paresis does not appear in the EU SmPC. Since launch, GSK is aware of 16 such cases.

Risk Management Plan

GSK will implement the Menveo European Risk Management Plan (EU RMP) (version 8.2, dated 18 April 2016) with an Australian Specific Annex (version 1.1, dated April 2017) both of which were submitted to the TGA on 28 April 2017.

Additionally, revisions to the EU RMP aligned to the responses provided to the TGA RMP evaluation, dated 28 April 2017, are currently in progress and GSK commits to submitting the revised EU RMP as a post approval commitment, as soon as available. GSK also agrees to submit final reports of ongoing post marketing safety studies (listed in ASA) when completed.

Product Information (PI) and Consumer Medicine Information (CMI)

GSK has considered the PI recommendations made by the TGA Delegate and our response is provided: A revised copy of the PI and CMI, annotated to include reference to changes required in the Delegates overview, clinical evaluation report and RMP evaluation report are provided with this response. GSK commits to liaising with the TGA Delegate to finalise the PI and CMI to the satisfaction of the TGA.

Conclusion

Current public health need in Australia and the available data package supports the need for Menveo to be registered for use in infants 2 months and over and children 2 years and over. This is supported by the TGA clinical evaluator, TGA Delegate and a recognised Australian expert on paediatric meningococcal disease.

The available data supports registration of Menveo administered as a 4 dose primary schedule in infants from 2 to 6 months, which also enables vaccination to be aligned with other infant vaccines given at the same time point. The data also supports a 2 dose catch up schedule in infants 7 to 23 months of age and a single dose vaccination schedule in children 2 years and over.

The safety profile of Menveo in Infants 2 months of age and over and children 2 years of age and over is consistent with the known safety profile of Menveo in other population cohorts and similar to that of Menactra which is also approved for use in children 2 years and over.

Advisory Committee Considerations

The Advisory Committee on Vaccines (ACV), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACV taking into account the submitted evidence of efficacy and safety agreed with the Delegate and considered Menveo meningococcal (Groups A, C, W-135 and Y) oligosaccharide CRM197 conjugate vaccine to have an overall positive benefit-risk profile for the extension of indication [as underlined]:

*Menveo is indicated for active immunisation of infants and children (from 2 months of age), adolescents 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*

and for dosing schedules, summarised as:

- infants initiating vaccination from 2 to 6 months of age - three primary doses, with an interval of at least 2 months; a fourth dose should be administered during the second year of life (at 12-16 months) ('3+1' schedule)
- unvaccinated children from 7 to 23 months of age - two doses, with the second dose administered in the second year of life
- children 2 to 10 years of age – one dose.

In making this recommendation the ACV:

- noted the changing epidemiology of meningococcal disease, with increasing notifications of W and Y serogroups, and low levels of A and C serogroups in Australia (although different epidemiological considerations will apply to travellers)
- noted the complex regimens, with the number of doses affected by age group at time of first vaccination and concomitant health conditions
- supported the use of a 3+1 schedule in infants
- supported the use of a 2 dose schedule in infants (Dose 1 at 7 months of age, Dose 2 in second year of life), as a catch-up ACWY vaccination strategy in unvaccinated infants
- supported the use of a 1 dose schedule in children aged 2 to 10 years.

Proposed Product Information (PI) / Consumer Medicine Information (CMI) amendments

The ACV suggested that the PI could highlight that serogroup A is very rare in Australia and that the immune response and immune persistence appears lower for serogroup A than for the other serogroups. This should be considered for infants travelling internationally to areas of different disease epidemiology.

Specific Advice

The ACV advised the following in response to the delegate's specific questions on the submission:

1. *Risk/Benefit of the proposed 4 dose (3+1) infant schedule (2, 4, 6 and 12-16 months of age).*

The ACV advised that the benefits of the proposed schedule were the additional coverage of serogroups W and Y and the earlier and non-inferior immunogenicity for serogroup C, when compared to the current national provision of immunisation against serogroup C only at age 12 months.

There is clear benefit of the booster in the second year of life, due to waning antibodies following the primary series in early infancy. The committee noted that as 16 months of age is not established as a routine time point in the National Immunisation Program Schedule, in practice infants would most likely be vaccinated at 12 months of age.

This 3+1 schedule is also suitable for infants at high risk (that is, immunocompromised infants).

Targeted long-term follow-up studies of persistence of immunity should be required.

To date, there is no clear safety signal that would lead the committee to advice against the proposed schedule. Overall, the risk/benefit of the proposed 4 dose infant schedule was favourable. The committee noted the sponsor's pre-ACV response.

2. *The suitability of a two-dose schedule based on the two-dose data in the Study V59V20 V59P20.*

Study V59P20 was the pivotal study in support of the single dose schedule for children aged 2 to 10 years who had not previously received a meningococcal vaccine. Menveo

resulted in higher immunogenicity for C, W and Y serogroups in children 2 to 10 years compared with Menactra (manufactured by Sanofi Pasteur).

The ACV advised that the proposed two-dose schedule may be suitable to provide maximum protection, especially in immunocompromised individuals.

One dose appeared to provide adequate protection in healthy individuals.

3. *Other issues that may be relevant to a decision on whether or not to approve this application*

The committee queried the status of post-marketing surveillance of administration of the vaccine during pregnancy (V59_720B); the Periodic Benefit Risk Evaluation Report stated that the study seeks to enrol 100 exposed pregnancies over a three-year period starting 30 September 2014 but that nil women had been enrolled as at February 2016.

The utility of the targeted follow-up questionnaire for acute disseminated encephalomyelitis, Guillain-Barre syndrome and vasculitis/Kawasaki syndrome was unclear but the signals did not seem to justify an active surveillance program at this time.

The ACV noted the surveillance data on vaccine failures provided by the sponsor in its pre-ACV response, and recommended that capture of vaccine failure data for the extended schedules in infants should be part of pharmacovigilance activities.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Menveo meningococcal (Groups A, C, W-135 and Y) oligosaccharide CRM197 conjugate vaccine and Menveo meningococcal (Groups A, C, W-135 and Y) oligosaccharide CRM197 conjugate vaccine, indicated for:

Menveo is indicated for active immunisation of infants and children (from 2 months of age), adolescents 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.

Specific conditions of registration applying to these goods

The Menveo Risk Management Plan (EU-RMP), version 8.2, dated 18 April 2016 (data lock point 14 March 2014) with Australian Specific Annex version 1.0, 26 April 2017 included with submission number PM-2017-00536-1-2, to be revised to the satisfaction of the TGA, and any future updates as a condition of registration.

Attachment 1. Product Information

The PI for Menveo approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

Attachment 2. Extract from the Clinical Evaluation Report

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