



Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Meningococcal (Groups A,C,W-135 and Y) oligosaccharide, CRM197 conjugate vaccine

Proprietary Product Name: Menveo

Sponsor: GlaxoSmithKline Australia Pty Ltd

28 March 2017

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About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
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List of 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.

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

1. Introduction

1.1. Identifying information

Submission number	PM-2017-00536-1-2
Sponsor	GlaxoSmithKline Australia Pty Ltd
Trade name	Menveo
Active substance	Meningococcal (Groups A,C,W-135 and Y) oligosaccharide CRM197 conjugate vaccine

1.2. Submission type

This is a Category 1 application for MenACWY (Menveo) to extend the indication to include immunisation of individuals 2 months of age and over. It is currently approved for use in adolescents and adults 11-55 years in Australia. The formulation used in the studies reviewed is unchanged and is the same as the approved formulation.

1.3. Drug class and therapeutic indication

MenACWY is a polysaccharide vaccine against 4 strains of *N. meningitidis* to prevent invasive meningococcal disease.

1.4. Information on the condition being treated

Meningococcal disease is caused by a gram-negative diplococcus, *Neisseria meningitidis*. *N. meningitidis* causes life-threatening disease worldwide. Based on antigenic variations in capsular polysaccharide structure, 13 serogroups of *N. meningitidis* have been identified. Globally, 5 serogroups, A, B, C, W-135 and Y, cause almost all invasive meningococcal infections. Invasive infection by *N. meningitidis* most often manifests as 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 B and C with few cases caused by serogroups A, W-135 and Y.¹ Children under 5 years of age and young adults aged 15 to 24 years are at the highest risk of acquiring meningococcal disease.

¹The recently published (in 2017) 'Meningococcal Disease National Surveillance Report' states that serogroup W followed by B and Y are now the most common in Australia. See [https://www.health.gov.au/internet/main/publishing.nsf/Content/5FEABC4B495BDEC1CA25807D001327FA/\\$File/Sept-2017-IMD-Surveillance-report.pdf](https://www.health.gov.au/internet/main/publishing.nsf/Content/5FEABC4B495BDEC1CA25807D001327FA/$File/Sept-2017-IMD-Surveillance-report.pdf)

1.5. Formulation

1.5.1. Formulation development

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

1.1. Guidance

This application was made after discussion by GSK with TGA and the Australian Health commission.

The use of immunogenicity data to support the effectiveness of meningococcal vaccines has been widely accepted in all previous international guidelines and registrations. It has been accepted by the Vaccines and Related Biological Products Advisory Committee (VRBPAC) as valid that a serological marker can be used to infer effectiveness of new meningococcal conjugate vaccines in children 2 years of age and older. In 2011, the committee also concluded that serum bactericidal activity with human complement (hSBA) could be used as an immune measure to infer effectiveness of meningococcal conjugate vaccines in children younger than 2 years of age. In addition, the committee concluded that sero-responses achieved at or above a pre-defined hSBA titre could be considered as evidence that the meningococcal-specific functional antibodies measured post-vaccination were protective against systemic infection

1.2. Evaluator's commentary on the background information

This application is to extend indication for MenACWY to children >2 months.

There is no change in formulation.

In contrast with the submission for individuals 11 to 55 which used single dose vaccination regimens, 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.

2. 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.

3. Contents of the clinical dossier

3.1. Scope 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 10 years of age

Infants/toddlers

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

- V59P14 and V59_33 supporting a 4-dose series infant schedule,
- V59P21 supporting a 2-dose series in children over 6 months of age who did not receive a 4-dose schedule,
- 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 2-10 years.

3.2. Paediatric data

All the studies included in this submission are paediatric.

3.3. Good clinical practice

During the original review of the data 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.

4. Pharmacokinetics

No new studies were submitted.

5. Pharmacodynamics

No new studies were submitted.

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

6. 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 and that 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.

7. Clinical efficacy

7.1. Studies providing evaluable 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 (Table 1). The pivotal immunogenicity and safety study supporting the 2-10 year age group is Study V59P20 a Phase III, randomised, observer-blind, multicentre study conducted in the US and Canada in children 2-10 years of age to compare the safety and immunogenicity of MenACWY with Menactra.

Table 1: Overview of Studies included in this submission

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
Studies for Proposed Indication:							
V59P7	Finland	Safety and Immune Response of MenACWY with and without Adjuvant vs Mencevax™	Observer-Blind, Randomized, Active Controlled	MenACWY 10-5-5-5og Ad-IM	205	Healthy Subjects	Two
	Poland		Phase 2	MenACWY 10-5-5-5og Ad-IM	331	Toddlers 12-35 m	
			Multi-Center	Mencevax™ IM followed by MenACWY 10-5-5-5og Ad- IM	81	Children 36-59 m	
V59P8	US	Safety and Immune Response of MenACWY vs Menomune™	Single-Blind, Randomized, Active Controlled	MenACWY 10-5-5-5og Ad-IM	453	Healthy Subjects	One
			Open-Label in Toddlers	MenACWY 10-5-5-5og Ad-(+ PnC) IM	71	Children 2-10 y	
			Phase 2 Single-Center	MenACWY 10-5-5-5og Ad-(+ DTaP) IM	73	Toddlers 12-23 m	
				Menomune™ SC	310		
V59P10	Argentina	Safety and Immune Response MenACWY vs Menomune™	Observer-Blind, Randomized, Active Controlled	MenACWY 10-5-5-5og Ad-IM	949	Healthy Subjects	One
			Phase 3	Menomune™ SC	551	Children 2-10 y	
			Multi-Center				
V59P20	US Canada	Safety and Immune response to MenACWY vs Menactra™	Observer-Blind, Randomized, Active Controlled	MenACWY 10-5-5-5og Ad-IM	1635	Healthy Subjects	One or Two
			Phase 3 Multi-Center	Menactra™	1268	Children 2-10 y	
V59P5	UK Canada	Safety and Immune Response Schedule Finding Two or Three Doses With Concomitant Infant Routine Vaccinations Persistence of Antibodies, Booster and Memory Response	Open-label, Randomized, Active Controlled	MenACWY 10-5-5-5og Ad+ with 10-5-5-5 og Ad+ Boost IM	229	Healthy Subjects	One, Three or Four
			Phase 2	MenACWY 10-5-5-5og Ad+ with no Boost IM	49	Infants 2 m	
			Multi-Center	MenACWY 10-5-5-5og Ad-IM followed by 1/5 th Dose Menomune™ SC	98		
				MenACWY 10-5-5-5og Ad+ with 10-5-5-5 og Ad- Boost IM	135		
				MenACWY 10-5-5-5og Ad-IM followed by 1/5 th Dose Menomune™ SC	45		
				Menjugate™ with MenACWY 10-5-5-5og Ad+ Boost IM	45		
V59P9	Canada	Schedule Finding Safety and Immune Response After One or Two Doses of MenACWY	Open Label, Partially Randomized, Active Controlled	MenACWY 10-5-5-5og Ad-IM	125	Healthy Subjects	One or Two
			Phase 2 Multi-Center	Menjugate™ followed by MenACWY 10-5-5-5og Ad-IM	50	Infants 6-12 m	

Table 1 continued: Overview of Studies included in this submission

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 10-5-5-5 μ g Ad-IM (1 Routine Vaccines)	3035	Healthy Subjects	Two or Three in Infants
	Argentina Colombia		Phase 3 Multi-Center	Routine Vaccines Only Followed by MenACWY 10-5-5-5 μ g Ad- IM	1521	Infants 2 m	One or Two in Toddlers
V59P21	US	Safety and Immune Response of ProQuad TM when administered with MenACWY	Open-Label, Randomized	MenACWY 10-5-5-5 μ g Ad-IM and ProQuad TM SC	500	Healthy Subjects	Two
			Phase 3 Multi-Center	MenACWY 10-5-5-5 μ g Ad-IM followed by ProQuad TM SC	502	Infants 7-12 m	
				ProQuad TM SC	599		
V59P23	US Taiwan Costa Rica Guatemala Peru Panama Saudi Arabia	Safety of MenACWY when administered with Routine infant vaccines	Open-Label, Randomized	MenACWY 10-5-5-5 μ g Ad-IM (1 Routine Vaccines)	~5775*	Healthy Subjects	Four
			Phase 3 Multi-Center	Routine vaccines only	~1925*	Infants 2 m	
V59_33	US Australia Canada	Safety and immune response of MenACWY when administered with Routine infant vaccines	Open-Label, Randomized	MenACWY 10-5-5-5 μ g Ad-IM (1 Routine Vaccines)	~260*	Healthy Subjects	Four
			Phase 3 Multi-Center	Routine vaccines only	~260*	Infants 2 m	

7.2. Pivotal or main efficacy studies

7.2.1. Study V59P14

7.2.1.1. Study design, objectives, locations and dates

This was a Phase III, randomised, open-label, multicentre, parallel-group study that enrolled healthy infants 2 months of age (55 to 89 days inclusive). The study was conducted in the US and Latin America (Argentina and Colombia) from March 2007 until November 2009.

Primary objectives

- To assess the immunogenicity of four doses of MenACWY given to infants at 2, 4, 6 and 12 months of age measured by the percentage of subjects with hSBA \geq 1:8, directed against *N. meningitidis* serogroups A, C, W and Y (US subjects).
- To compare the immunogenicity of the fourth dose of MenACWY given at 12 months of age in subjects who previously received three doses of MenACWY given at 2, 4 and 6 months of age to the immunogenicity of a single dose of MenACWY given to naïve subjects at 12 months of age, as measured by the ratio of GMTs, directed against *N. meningitidis* serogroups A, C, W, and Y (US subjects);

Secondary objectives

- To assess the immunogenicity of three doses of MenACWY given to infants at 2, 4 and 6 months of age as measured by hSBA GMTs and by the percentage of subjects with hSBA \geq 1:8 and \geq 1:4, directed against *N. meningitidis* serogroups A, C, W and Y (US subjects);
- To compare the immunogenicity of two doses of MenACWY given to infants at 2 and 6 months of age to three doses of MenACWY given to infants at 2, 4, and 6 months of age

as measured by hSBA GMTs and by the percentage of subjects with hSBA $\geq 1:4$ and hSBA $\geq 1:8$, directed against *N. meningitidis* serogroups A, C, W, and Y (Latin American [LA] subjects)

- c. To demonstrate that the immunogenicity of routine infant vaccines (that is, DTaP, IPV, HBV, pneumococcal conjugate, Hib), when given concomitantly with MenACWY at 2 and 6 or 2, 4 and 6 months of age, is non-inferior to that of routine infant vaccines given without MenACWY (US and LA subjects, assessed separately);
- d. To assess the persistence of bactericidal antibodies at 12 or 16 months of age in subjects who previously received two or three doses of MenACWY at 2 and 6 or 2, 4 and 6 months of age, as measured by hSBA GMT, hSBA $\geq 1:4$, and hSBA $\geq 1:8$, directed against *N. meningitidis* serogroups A, C, W, and Y (US and LA subjects, assessed separately);
- e. To assess the immunogenicity of the third or fourth dose of MenACWY given at 12 or 16 months of age in subjects who previously received two or three doses of MenACWY given at 2 and 6 or 2, 4 and 6 months of age, as measured by hSBA GMT, hSBA $\geq 1:4$, hSBA $\geq 1:8$, and hSBA $\geq 1:16$, directed against *N. meningitidis* serogroups A, C, W, and Y (US and LA subjects, assessed separately);
- f. To demonstrate the immunogenicity of routine booster vaccinations given in the second year of life (that is, pneumococcal conjugate booster, Hib) when given concomitantly with MenACWY (US and LA subjects, assessed separately) as shown in Table 2.

Table 2: Concomitant Vaccine Antigen Test Types and Key Secondary Immunogenicity Endpoints of Pivotal Study V59P14

Vaccine	Test	Antigens	Threshold (infant series)	Endpoints	Threshold (toddler dose)	Endpoints
Pediarix (at 7 moa ^b) Infanrix ^c (at 17 moa ^b)	ELISA	Diphtheria	≥ 0.1 IU/mL	% \geq threshold	≥ 1.0 IU/mL	% \geq threshold
	ELISA	Tetanus	≥ 0.1 IU/mL	% \geq threshold	≥ 1.0 IU/mL	% \geq threshold
	ELISA	PT FHA PRN	Seroresponse: if baseline \geq LLQ, 4-fold increase over baseline; if baseline <LLQ, $\geq 4x$ LLQ	GMC ratio and % with seroresponse	Seroresponse: if baseline \geq LLQ, 4-fold increase over baseline; if baseline <LLQ, $\geq 4x$ LLQ	GMC ratio and % with seroresponse
Pediarix (at 7 moa)	NT	Poliovirus type 1 Poliovirus type 2 Poliovirus type 3	$\geq 1:8$	% \geq threshold		
	ELISA	HBV	≥ 10 mIU/mL	% \geq threshold		
ActHIB (at 7 and 17 moa)	ELISA	Hib (PRP)	≥ 0.15 μ g/mL	% \geq threshold	≥ 1.0 μ g/mL	% \geq threshold
Prenar (at 7 and at 13 moa)	ELISA	PnC 4 PnC 6B PnC 9V PnC 14 PnC 18C PnC 19F PnC 23F	≥ 0.35 μ g/mL	% \geq threshold GMC ratio	≥ 1.0 μ g/mL	GMC ratio and % \geqthreshold

moa=months of age; IU=international units; LLQ=lower limit of quantification; a key secondary endpoints as analysed in study V59P14 are indicated in bold italics. B for the 3 pertussis antigens, baseline titres were also measured at 2 and 16 months in order to assess seroresponse; c: Infanrix and ActHIB at 17 moa were assessed in the LA part of the study only, using the following additional supportive endpoints not tabulated here: GMC ratios for diphtheria, tetanus, and Hib (non-inferiority criterion=LL of the 95% CI of the GMC ratio>0.5).

Study V59P14 also assessed the immunogenicity of MenACWY administered at 2, 4, 6, and 12 or 16 months of age, the immunogenicity of a 2-dose toddler catch-up schedule, with MenACWY administered at 12 months and at 15 months of age, and the effect of co-administration of MenACWY on the immunogenicity of:

- i. routine infant vaccines DTaP-HBV-IPV (Pediarix), Hib (ActHIB) and PCV7 (Prenar); and
- ii. routine toddler vaccines (Prenar, DTaP [Infanrix], and ActHIB).

Overall there were a total of 13 vaccine groups in this study, including nine which provided immunogenicity data and four which supported safety analyses only. The design is shown in horizontally and also in terms of age breakdown within the groups in Tables 3-5.

Table 3: Design of Study V59P14

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)	
V59P14						
V59P14 US study groups						
Assessment of immunogenicity: MenACWY 4-dose series, immunogenicity including persistence, memory, and concomitant use with other routine pediatric vaccines Assessment of safety/tolerability	Randomized, open-label, parallel, multicenter	2 months, US	US1A	2, 4, 6, 12	2, 4, 6, 12 ^a	154
			US1B	2, 4, 6, 13	2, 4, 6, 12 ^a	166
			US2	12, 15 ^b	2, 4, 6, 12 ^a	159 ^f
			US3	2, 4, 6, 12	2, 4, 6, 12 ^a	650
			US4A	12, 15	2, 4, 6, 12 ^a	76
			US4B	13, 15	2, 4, 6, 12 ^a	70
			US4C	15	2, 4, 6, 12 ^a	203
V59P14 LA study groups						
		2 months, Latin America (Argentina and Colombia)	LA1A	2, 6, 12	2, 4, 6, 12 ^a	151
			LA1B	2, 6, 13	2, 4, 6, 12 ^a	150
			LA2	12, 15 ^b	2, 4, 6, 12 ^a	148
			LA3A	2, 4, 6, 16	2, 4, 6, 12 ^a , 16 ^c	151
			LA3B	2, 4, 6, 17	2, 4, 6, 12 ^a , 16 ^c	150
			LA4	12, 15 ^d	2, 4, 6, 12 ^a , 15 ^e	150
			<i>LA5</i>	2, 4, 6, 12	2, 4, 6, 12 ^a	1426
			<i>LA6A</i>	12, 15	2, 4, 6, 12 ^a	358
			<i>LA6B</i>	13, 15	2, 4, 6, 12 ^a	170
			<i>LA6C</i>	15	2, 4, 6, 12 ^a	183

mos=months; the groups pertinent to this ISE are in indicated in bold italics; within this dossier, study V59P7 contributed only to the immunogenicity assessments while study V59P8 contributed only to the pooled safety analyses. a subjects' age (in months) at the time of MenACWY vaccinations (study groups pertaining to data in this ISE); b MenACWY Ad+ = adjuvanted MenACWY formulation; MenACWY= unadjuvanted, final MenACWY formulation; c routine vaccines were also administered according to the country-specific vaccination programs/schedules; d subjects > 24 months of age; e only subjects 24 months of age or younger are included in the immunogenicity discussion in this dossier;. f only subjects 23 months of age or younger are tabulated here since included in the pooled safety analysis in this dossier.

Table 4: Study Design, Pivotal Study V59P14, LA Immunogenicity Groups LA3 and LA4, size and age

Groups, No. of Subjects Enrolled		Months of Age				Sub Groups	Months of Age				
	Vaccines	2	4	6	7		12	13	15	16	17
LA3 N=301	Men ACWY + routine vaccines	Serology	Infant routine vaccines ^a	Infant routine vaccines ^a	Serology	LA3A N=151	Toddler routine vaccines ^b	N/A	N/A	Serology	Serology
		Infant routine vaccines ^a	Men ACWY	Men ACWY	MenACWY					Toddler routine vaccines ^c	
		Men ACWY				LA3B N=150	Toddler routine vaccines ^b	N/A	N/A	Serology	Serology
										Toddler routine vaccines ^d	MenACWY
LA4 N=150	Routine vaccines	Serology	Infant routine vaccines ^a	Infant routine vaccines ^a	Serology		Serology	N/A	Men ACWY	Serology	
		Infant routine vaccines ^a					Toddler routine vaccines ^b		Toddler routine vaccines ^c		
							MenACWY				

Table 5: Pivotal Study V59P14, US Immunogenicity Groups, size and age

Groups, Number of Subjects Enrolled		Months of Age				Groups, Subjects Enrolled	Months of Age		
	Vaccines Administered	2	4	6	7		12	13	15
US1 N=320	MenACWY + routine vaccines	Serology			Serology	US1A N=154	Serology	Serology	
		Infant routine vaccines ^a	Infant routine vaccines ^a	Infant routine vaccines ^a			Toddler routine vaccines ^b		N/A
		MenACWY	MenACWY	MenACWY		US1B N=166	Serology	Serology	
							Toddler routine vaccines ^b	MenACWY ^c	N/A
US2 N=159	Routine vaccines	Serology	Infant routine vaccines ^a	Infant routine vaccines ^a	Serology		Serology	Serology	
		Infant routine vaccines ^a					Toddler routine vaccines ^b		
							MenACWY		MenACWY ^c

a infant routine vaccines: ActHIB, Pediarix, Prevnar, and RotaTeq; b toddler routine vaccines: ProQuad, Prevnar, and Havrix; c a safety follow-up call was performed 6 months after the last MenACWY injection.

Note: Blood samples for serology testing were taken before scheduled vaccinations; MenACWY (when administered at 13 and 15 months of age), RotaTeq, Havrix, and ProQuad were not analysed for immunogenicity

7.2.1.2. Inclusion and exclusion criteria

Inclusion Criteria

- Healthy 2 month old infants (aged 55-89 days), born after a full-term pregnancy with an estimated gestation age >37 weeks and a birth weight > 2.5kg
- Parent/legal representative has given written informed consent
- Available for all visits scheduled in the study
- Who were in good health as determined by investigator

Exclusion Criteria

- Previously had received any meningococcal vaccine or DTP, IPV, or OPV, H. influenza type b (Hib) or Pneumococcus (birth doses of BCG (one) and/or HBV (two) were permitted)
- Previous confirmed or suspected disease caused by *N. meningitides*, *C. diphtheriae*, *C. tetani*, Poliovirus, Hepatitis B, Hib, Pneumococcus or *B. pertussis* (history of laboratory confirmed, or clinical condition of paroxysmal cough for a period of longer than or equal to 2 weeks associated with apnoea or whooping)
- Household contact with and/or intimate exposure to an individual with laboratory confirmed *N. meningitidis* (serogroups A, C, W135, or Y), *B. pertussis*, Hib, *C. diphtheriae*, polio, or pneumococcal infection at any time since birth
- History of anaphylactic shock, asthma, urticaria, or other allergic reaction after previous vaccinations or known hypersensitivity to any vaccine component
- Significant acute or chronic infection within the previous 7 days or have experienced fever (temperature >38.0C [100.4F]) within the previous 3 days
- Any present or suspected acute (for example, leukaemia, lymphomas), or chronic disease (for example, seizure disorder, cardiac disease, renal failure, severe malnutrition, or insulin dependent diabetes), progressive neurological disease, immunosuppression, or a genetic anomaly/known cytogenetic disorders (for example, Down Syndrome)
- Known or suspected autoimmune disease or persistent impairment/alteration of immune function resulting from (for example) receipt of any immunosuppressive therapy at any time since birth, any immunostimulants at any time since birth, or any systemic corticosteroid since birth.
- Suspected or known HIV infection or HIV related disease
- Prior receipt of blood, blood products, and/or plasma derivatives or any parenteral immunoglobulins
- Known bleeding diathesis, or any condition that may be associated with a prolonged bleeding time
- History of seizure
- Planning to leave the area of the study site before the end of the study period
- Any condition which, in the opinion of the investigator, might interfere with the evaluation of the study objectives
- Prior receipt of any investigational agents or vaccines since birth or who expected to receive an investigational agent or vaccine prior to the completion of the study
- Relatives of site research staff working on this study

Withdrawal or Discontinuation

Subjects did not receive further study vaccinations for any of the following:

- Development of exclusion criteria
- Any serious vaccine-related reaction to investigational or concomitant vaccines
- Febrile convulsions or neurologic disturbance after vaccination
- Hypersensitivity to the investigational vaccine
- Other suspected side effect that could compromise the subjects' well being

7.2.1.3. Study treatments

Investigational vaccine

- MenACWY: Each 0.5 mL dose contains 10 µg MenA oligosaccharide, 5 µg of each of MenC, MenY and MenW-135 oligosaccharides and a total of 32.7 to 64.1 µg of CRM197 protein.
- The vaccine contains no preservative or adjuvant.
- Given intramuscularly (IM).

Concomitant vaccines

Subjects enrolled received concomitant routine infant vaccinations as recommended by the Advisory Committee on Immunization Practices (ACIP) in the USA or equivalent in other countries. This included DTaP-IPV-Hib vaccine (Pentacel; Aventis Pasteur, Inc), 7-valent pneumococcal conjugate vaccine (Pneumovax 7; Pfizer, Inc), MMR vaccine (MMR-II; Merck & Co, Inc), Rotavirus (Rotateq, Merck & Co., Inc), Hepatitis B (Recombivax HB), Varicella (Varivax, Merck & Co., Inc), and a Hepatitis A virus vaccine.

7.2.1.4. Efficacy variables and outcomes

In all studies, immunogenicity of MenACWY was tested at the centralized Novartis laboratory using a validated serum bactericidal assay using human complement (hSBA). The selection of the serum bactericidal assay was based on the Vaccines and Related Biological Products Advisory Committee (VRBPAC) opinion (1999) that immunological correlates can be used to predict efficacy of meningococcal vaccines and the presence of bactericidal antibodies can be used as a surrogate marker of protection against meningococcal disease.

Overall, the endpoints used to support the claim of efficacy for MenACWY in this application are: (i) hSBA \geq 1:8, (ii) hSBA Geometric Mean Titres (GMTs); and (iii) Reverse Cumulative Distribution Functions (RCDF) curves. In accordance with the immunogenicity objectives/statistical criteria used in the 3 pivotal studies, the main focus is on the adequacy of the antibody responses to MenACWY expressed in terms of the percentages of subjects with hSBA \geq 1:8.

In all studies presented in the current submission, immunogenicity of MenACWY was assessed approximately 1 month following the vaccination under evaluation, the only exception being the MenACWY dose administered at 12 months of age in Study V59P21: because in this study an MMRV vaccine was given at 12 months of age, immune responses for both the MMRV vaccine and MenACWY were analysed at 6 weeks post-vaccination (optimal period for measuring immunogenicity of the MMRV antigens).

7.2.1.5. Randomisation and blinding methods

In all studies, healthy subjects were enrolled and randomised to vaccine groups according to a randomisation list either generated or specified by the Novartis Vaccine Biostatistics and Statistical Reporting (B&SR) unit. These studies were open and not blinded.

7.2.1.6. Analysis populations

In all studies in this submission, the populations analysed were defined based on similar subject inclusion/exclusion rules. The modified intention-to-treat (MITT) population included all subjects who received at least one dose of the study vaccine and provided at least one evaluable post vaccination serum sample for immunogenicity assessments. In the 3 supportive studies and in the MMRV immunogenicity analyses in pivotal Study V59P21, an evaluable serum sample at baseline was also a requirement for inclusion in the MITT population. In all studies, the per-protocol (PP) population consisted of MITT subjects who received all study vaccines in accordance with the protocol, provided serum samples as scheduled for the time points under evaluation, and had no major protocol deviations relevant to the endpoint under evaluation

7.2.1.7. Sample size

Approximately 4500 infants 2 months of age (55 89 days inclusive) were planned to be enrolled and randomised open-label to treatment in a 2:1 ratio, (MenACWY + routine infant vaccines: routine infant vaccines only), stratified by study site, and geographic region (also in a 2:1 ratio, Latin America: US). Overall approximately 3000 subjects were planned to receive MenACWY together with routine infant vaccines and 1500 subjects were planned to receive the routine infant vaccines alone. All 4500 subjects were planned to receive at least one dose of MenACWY at some point during the study.

7.2.1.8. Statistical methods

Table 6 presents the statistical criteria used in the 3 pivotal immunogenicity studies to demonstrate adequacy of the immune responses elicited by the proposed:

- 4-dose MenACWY series (co-primary objective in Studies V59P14 and V59_33 and secondary objective in the LA part of Study V59P14); and
- 2-dose catch-up schedules (co-primary objective in Study V59P21 and secondary objective in the LA part of Study V59P14).

Table 6: Criteria for Demonstrating Adequacy of Immune Responses Elicited by MenACWY, Percentage of Subjects with hSBA \geq 1:8, Pivotal Studies V59P14, V59_33 and VP5921c

Study	Criteria for demonstrating adequate immune response
V59P14 ^a (4-dose series)	Lower limit (LL) of the 2-sided 95% confidence interval (CI) around the percentage of subjects achieving a post-4 th dose hSBA \geq 1:8 \geq 80% for serogroup A and \geq 85% for serogroups C, W, and Y
V59_33 ^b (4-dose series)	LL of the 2-sided 95% CI around the percentage of subjects achieving a post-4 th dose hSBA \geq 1:8 $>$ 80% for serogroup A and $>$ 85% for serogroups C, W, and Y
V59P21 ^c (2-dose catch-up ^d)	LL of the 2-sided 95% CI around the percentage of subjects achieving a post-2 nd dose hSBA \geq 1:8 \geq 65% for serogroup A and \geq 85% for serogroups C, W, and Y

a co-primary immunogenicity objective in Study group US1A and secondary immunogenicity objective (no protocol-defined statistical criteria) in Study group LA3A; an additional statistical criterion was used in study V59P14 (second co-primary immunogenicity objective): superiority of the immune response to the 4th dose of MenACWY administered at 12 months of age versus the 1st dose of MenACWY administered at 12 months of age would be declared if the LL of the 95% CI around the GMT ratio (4th dose:1st dose) was $>$ 2. b primary immunogenicity objective, study group MenACWY+R; c co-primary immunogenicity objective, study group MenACWY (receiving MenACWY only at 7-9 and 12 months of age; if the \geq 65% threshold for serogroup A was achieved, immune response would additionally be evaluated using the stricter, \geq 80% threshold, used after 4 doses in study V59P14); d immune response to a 2-dose catch-up schedule was also descriptively assessed in V59P14 Study group LA4 (hSBA GMTs and percentages of subjects with hSBA \geq 1:8 and \geq 1:4).

Statistical criteria for demonstrating adequacy of the immune response were first defined for the complete 4-dose series in Study V59P14, based on regulatory feedback. Subsequently, the statistical criteria for demonstrating adequacy of the immune response were defined for Study V59_33 based on CBER's request. Statistical criteria for the adequacy of the immune response for the 2-dose MenACWY series in Study V59P21 were defined by Novartis in the US (Table 8). No statistical criteria for the adequacy of the immune response were defined for the analyses of the 2-dose catch-up schedules in Study V59P14 or in supportive Studies V59P7 and V59P9.

For immune responses evaluated in terms of percentages of subjects achieving predefined antigen-specific antibody concentrations/titres, non-inferiority of the co-administration of the routine vaccines with MenACWY versus their administration alone was demonstrated if the LL of the 2-sided 95% CI around the difference in the percentages (concomitant minus non-concomitant groups) was $>$ -10%, or, in the case of the poliovirus types, measles, mumps, and

rubella, >-5%. For the immune responses evaluated in terms of GMC/GMT ratios, non-inferiority of the co-administration of the routine vaccines with MenACWY versus their administration alone was established if the LL of the 2-sided 95% CI around GMC/GMT ratio (concomitant: non-concomitant groups) was > 0.5, or, for the pertussis antigens, > 0.67. These key endpoints for the concomitant vaccinations are shown in Table 2.

7.2.1.9. Participant flow

Overall, a total of 4545 infants were enrolled into this study, including 1508 subjects from the US, 1530 subjects from Argentina, and 1507 subjects from Colombia.

US Immunogenicity Subjects

A total of 479 subjects were enrolled in the US immunogenicity groups US1 and US2. Out of the enrolled subjects, 351 subjects completed the study. The major reason for premature withdrawal was withdrawal of consent by 33 out of 320 (10%). Other reasons for premature withdrawal included adverse events, lost to follow-up, inappropriate enrolment, administrative reasons and protocol deviations/violations.

US Safety Subjects

A total of 1029 subjects were enrolled in the US safety groups US3 and US4. Out of the enrolled subjects, 801 subjects completed the study, with similar reasons for withdrawal to the immunogenicity group.

LA Immunogenicity Subjects

A total of 900 subjects were enrolled in the LA immunogenicity groups LA1, LA2, LA3 and LA4. Subjects were only enrolled into the LA immunogenicity groups from Argentina. Colombia did not contribute any subjects to these cohorts. Out of the enrolled subjects, 825 subjects completed the study. The percentages of subjects with premature withdrawals ranged from 4% - 18% across the vaccination groups. The major reason for premature withdrawal was withdrawal of consent by 3% - 9% subjects. Other reasons included adverse events, lost to follow-up, inappropriate enrolment, administrative reasons and protocol deviations/violations.

LA Safety Subjects

A total of 2137 subjects were enrolled in the LA safety groups LA5 and LA6. Out of the enrolled subjects, 1877 subjects completed the study. The major reasons for premature withdrawal were lost to follow up (5%) and withdrawal of consent (3%). Other reasons included adverse events, inappropriate enrolment, administrative reasons and protocol deviations/violations.

7.2.1.10. Major protocol violations/deviations

Subjects with major protocol deviations who provided blood draw at a time point are included in the MITT analysis for that time point. Minor protocol deviations did not result in subject exclusion from any analysis set. Most of the subjects had at least one protocol deviation and most of the deviations were minor. The major protocol deviations were mostly as a result of no vaccination/ blood draw and vaccination/ blood draw being out of the time window. In US immunogenicity subjects, 84%-94% subjects reported protocol deviations out of which 52%- 65% were classified major protocol deviations. In LA immunogenicity subjects, 61%- 82% subjects reported protocol deviations out of which 18% - 42% were major protocol deviations. The number, type and distribution of protocol deviations in this randomised study, including major deviations, were not thought to have meaningful implications for interpretation of the study results.

7.2.1.11. Baseline data

The demographic and other baseline characteristics were balanced across different vaccination groups. The majority of the population consisted of Caucasians (52% to 61% in immunogenicity subjects and 55% to 76% in safety subjects), while the rest of the population consisted of

Asians, Blacks, Hispanics and others. Although sex ratios were similar across the vaccination groups, the immunogenicity subjects consisted of more males than females (differences ranging from 10% to 14%). Age, height and weight were similar across the vaccination groups.

7.2.1.12. Results for the primary efficacy outcome

Key results for primary efficacy outcomes of the pivotal efficacy studies in infants/toddlers are shown in Table 7.

Table 7: Key results of pivotal studies V59_P14 and V59_33

Serogroup		2, 4, 6, 12 months of age				2, 4, 6, 16 months of age	
		Study V59P14 – US subjects		Study V59_33		Study V59P14 – Latin America subjects	
		Post 3 rd dose	Post 4 th dose	Post 3 rd dose	Post 4 th dose	Post 3 rd dose	Post 4 th dose
A		N = 212	N = 84	N=202	N=168	N=268	N=120
	% ≥1:8 95% CI	67 (61, 74)	94 (87*, 98)	76 (69, 81)	89 (83*, 93)	89 (85, 93)	95 (89, 98)
C	GMT 95% CI	2, 4, 6, 12 months of age				2, 4, 6, 16 months of age	
		Study V59P14 – US subjects		Study V59_33		Study V59P14 – Latin America subjects	
		Post 3 rd dose	Post 4 th dose	Post 3 rd dose	Post 4 th dose	Post 3 rd dose	Post 4 th dose
C		N = 204	N = 86	N=199	N=156	N=272	N=122
	% ≥1:8 95% CI	97 (93, 99)	98 (92*, 100)	94 (90, 97)	95 (90*, 98)	97 (94, 99)	98 (94, 100)
C		N = 204	N = 86	N=199	N=156	N=272	N=122
	GMT 95% CI	108 (92, 127)	227 (155, 332)	74 (62, 87)	135 (107, 171)	150 (127, 177)	283 (225, 355)
W-135	GMT 95% CI	2, 4, 6, 12 months of age				2, 4, 6, 16 months of age	
		Study V59P14 – US subjects		Study V59_33		Study V59P14 – Latin America subjects	
		Post 3 rd dose	Post 4 th dose	Post 3 rd dose	Post 4 th dose	Post 3 rd dose	Post 4 th dose
W-135		N = 197	N = 85	N=194	N=153	N=264	N=112
	% ≥1:8 95% CI	96 (93, 99)	100 (96*, 100)	98 (95, 99)	97 (93*, 99)	98 (96, 100)	100 (97, 100)
W-135		N = 197	N = 85	N=194	N=153	N=264	N=112
	GMT 95% CI	100 (86, 116)	416 (288, 602)	79 (67, 92)	215 (167, 227)	182 (159, 208)	727 (586, 903)
Y	GMT 95% CI	2, 4, 6, 12 months of age				2, 4, 6, 16 months of age	
		Study V59P14 – US subjects		Study V59_33		Study V59P14 – Latin America subjects	
		Post 3 rd dose	Post 4 th dose	Post 3 rd dose	Post 4 th dose	Post 3 rd dose	Post 4 th dose
Y		N = 182	N = 84	N=188	N=153	N=263	N=109
	% ≥1:8 95% CI	96 (92, 98)	100 (96*, 100)	94 (89, 97)	96 (92*, 99)	98 (96, 99)	99 (95, 100)
Y		N = 182	N = 84	N=188	N=153	N=263	N=109
	GMT 95% CI	73 (62, 86)	395 (269, 580)	51 (43, 61)	185 (148, 233)	125 (107, 146)	590 (463, 751)

US Immunogenicity results

A total of 479 subjects were enrolled in the immunogenicity groups US1 (US1A+US1B) and US2. The PP population included 323 subjects from the infant series and 267 subjects after toddler vaccination.

Primary Analysis

One month post-toddler vaccination at 13 months, 100% of subjects who received the fourth MenACWY dose at 12 months (US1A) achieved an hSBA titre ≥ 1:8 against serogroups W and Y, while 94% and 98% of subjects achieved an hSBA titre ≥ 1:8 against serogroups A and C, respectively. The lower limit of the two-sided 95% CI were greater than 80%, 85%, 85% and 85% (criteria for assessment) for MenA, MenC, MenW and MenY, respectively. Similarly, as part of the secondary analysis, 100% of subjects achieved an hSBA titre ≥ 1:16 against serogroups W and Y while 90% and 95% subjects achieved an hSBA titre ≥ 1:16 against serogroups A and C, respectively. Thus, co-primary endpoint 1 was met.

One month post-toddler vaccination at 13 months, the hSBA GMTs ranged from 77 - 416 against the four meningococcal serogroups. The ratios of hSBA GMTs of subjects who received a fourth MenACWY dose at 12 months (US1A) compared to the hSBA GMTs of the subjects who received the first MenACWY dose at 12 months (US2) ranged from 4.53 to 38 against the four meningococcal serogroups with the lower limit of 95% CI being greater than 2.0 against all of the serogroups. Thus, co-primary endpoint 2 was also met.

7.2.1.13. Results for other efficacy outcomes*US Secondary Analysis*

- Pre-infant series (at 2 months), hSBA GMTs ranged from 2.11 to 3.07 against the four meningococcal serogroups in subjects who received three infant-series doses of MenACWY (US1) group and were similar to those in the control group (US2; range 2.1 to 2.71). One month post-infant series vaccination, the hSBA GMTs in US1 increased significantly and ranged from 13 to 108. By contrast, the hSBA GMTs in US2 group remained unchanged (range 2.03 to 2.12) post infant series.
- Pre-infant series (at 2 months), the percentages of subjects with an hSBA titre $\geq 1:8$ against the four meningococcal serogroups who received three infant-series doses of MenACWY (US1) ranged from 2% to 17% and were similar to those in the control group (US2; range 3% - 11%). One month post-infant series vaccination, the percentages of subjects with an hSBA titre $\geq 1:8$ in US1 group increased significantly and ranged from 67% to 97%. By contrast, the percentages of subjects with an hSBA titre $\geq 1:8$ in US2 remained low (range 0 to 2%) following the series of routine infant vaccinations.
- One month post-infant series vaccination (7 months), the GMCs for pertussis and pneumococcal antigens in the subjects who received MenACWY concomitantly with routine infant vaccines (US1) were non-inferior to those in subjects who received only routine infant vaccines (US2), as shown in Table 8.

Table 8: Pivotal studies V59P14 and V59_33 - Non-interference of MenACWY on Concomitant Infant Routine Antigens, Non-inferiority Criteria Met/Failed for Key Secondary Endpoints

Vaccine Antigen Tested	V59P14 US	V59P14 LA	V59_33	
Diphtheria	√	√	√	√
Tetanus	√	√	√	√
Pertussis Antigens				
PT	√	√	√ ^a	∅ ^b
FHA	√	√	√ ^a	√ ^b
PRN	√	∅	√ ^a	√ ^b
FIM	N/A	N/A	√ ^a	∅ ^b
Polio serotypes				
1	√	√	√	√
2	√	√	√	√
3	√	√	√	√
HBV	√	√	√	√
Hib	√	√	√	√
Pneumococcal Antigens				
PnC 4	√	√	√	√
PnC 6B	∅	√	∅ ^c	∅ ^c
PnC 9V	√	√	√	√
PnC 14	√	√	√	√
PnC 18C	√	√	√	√
PnC 19F	√	√	√	√
PnC 23F	√	√	√	∅ ^c

N/A=not applicable;

- One month post-infant series vaccination (7 months), in those who received MenACWY and routine vaccines (US1) the seroresponse rates against polio, PT, FHA, diphtheria, tetanus, hepatitis B, Hib and 6 of 7 pneumococcal antigens were non-inferior to those in subjects who received only routine infant vaccines (US2). The non-inferiority criteria for vaccine response were not met only for seroresponse for pertactin and PnC 6B (unlikely to be clinically relevant).

- At 12 months, 12% to 69% of the subjects, who had previously received three doses of MenACWY (US1), had persistence of an hSBA titre \geq 1:8 against the four meningococcal serogroups whereas only 1% to 7% subjects, who did not have any previous MenACWY vaccination (US2), had hSBA titre \geq 1:8
- One month post-toddler vaccination (13 months), the GMCs for pneumococcal antibodies in the subjects who received pneumococcal conjugate booster vaccine concomitantly with a fourth dose of MenACWY at 12 months (US1A) were non-inferior to those in subjects who received only pneumococcal conjugate booster vaccine at 12 months (US1B). One month post-toddler vaccination (13 months), the non-inferiority criteria for percentages of subjects with antibody concentration \geq 1.0 $\mu\text{g/mL}$ against pneumococcal antigens in the subjects who received pneumococcal conjugate booster vaccine concomitantly with fourth dose of MenACWY at 12 months (US1A) were non-inferior (lower limit of two sided 95% CI of the difference $>$ -10%) to those in subjects who received only pneumococcal conjugate booster vaccine at 12 months (US1B) for 4 of the 7 pneumococcal serotypes (PnC 4, PnC 6B, PnC 14 and PnC 19F). Non-inferiority criteria were met for all serotypes when assessing those with antibody concentrations \geq 0.35 $\mu\text{g/mL}$.
- In subjects who received the first MenACWY vaccination at 12 months (US2; 1st toddler vaccination), the hSBA GMTs increased from the range of 2.14-2.26 (pre-toddler vaccination) to the range of 10-35 (one-month post-toddler vaccination) against the four meningococcal serogroups; the percentages of subjects with hSBA titre \geq 1:8 increased from the range of 1%-7% (pre-toddler vaccination) to the range of 56% - 90% (one-month post-toddler vaccination).

7.2.1.14. Evaluator commentary

The primary analysis of the study was intended to support an indication for a 4-dose MenACWY vaccination series at 2, 4, 6 and 12 months of age. After the four dose series, the pre-specified primary immunogenicity criteria were achieved both in terms of the percentages of subjects achieving an hSBA titre \geq 1:8 and the ratio of GMTs against the serogroups MenA, MenC, MenW and MenY of a 4th dose of MenACWY versus a 1st dose of MenACWY in a naive age-matched control group. At least 94% of subjects achieved an hSBA titre \geq 1:8 to each of the serogroups at 13 months of age after the 12 month vaccination. Assessment of interference with the immune response to concomitant infant vaccines (that is, DTaP, IPV, Hib, HBV, and pneumococcal) was assessed as a secondary objective. Compared to routine infant vaccines given alone, non-inferiority of the antibody response to each of the vaccine antigens was demonstrated for the routine vaccines when administered with MenACWY. The only exceptions were for seroresponse to pneumococcal serotype 6B and for 4-fold rise for pertactin, although the GMC ratio non-inferiority objectives were achieved for both antigens.

In the second year of life, the immune response as measured by GMC ratio to pneumococcal antigens was non-inferior for all serotypes when the pneumococcal conjugate vaccine was administered concomitantly with MenACWY, MMR-V and HAV when compared to the three vaccines given together without MenACWY. Using criteria of percentages of subjects with antibody concentration \geq 1.0 $\mu\text{g/mL}$, non-inferiority was achieved for 4 of the 7 serotypes; and using the \geq 0.35 $\mu\text{g/mL}$ criteria, non-inferiority was achieved for all serotypes.

7.2.2. Study V59_33

7.2.2.1. Study design, objectives, locations and dates

This was a Phase III, open-label, randomised, controlled multicentre study that enrolled healthy infants 2 months of age (55 to 89 days inclusive). The study was conducted from November 2009 to November 2011 at 42 study sites in the US, 3 sites in Australia, and a single Canadian centre. The study enrolled 529 infants at a 1:1 ratio to receive either MenACWY concomitantly

with routine infant/toddler vaccines (N=258) or routine infant/toddler vaccines alone (N=271). Subjects were randomised in a 1:1 ratio into one of two study groups as follows:

- Group 1 (ACWY+R): subjects received MenACWY with routine concomitant vaccinations at 2, 4, 6 and 12 months of age.
- Group 2 (Routine): subjects only received routine vaccinations at 2, 4, 6, and 12 months of age. Group 2 subjects also were offered one dose of MenACWY at 18 months of age as a benefit of participating in the study.

The V59_33 study design is shown in Table 9.

Table 9: Study V59_33 - Design and objectives

Group, Number of Subjects Enrolled	Months of Age					
	2	4	6	7	12	13
MenACWY+Routine vaccines (MenACWY+R) N=258	Serology MenACWY Routine infant vaccines ^a	MenACWY Routine infant vaccines	MenACWY Routine infant vaccines	Serology	Serology MenACWY Routine toddler vaccines	Serology
Routine vaccines only (Routine) N=271	Serology Routine infant vaccines	Routine infant vaccines	Routine infant vaccines	Serology	Serology Routine toddler vaccines	Serology

a routine infant vaccines were: Pentacel, Prevnar, and commercially available (US-licensed) HBV, if a birth dose of HBV was administered, at 4 months of age, the HBV dose could be omitted according to local practices; commercially available rotavirus vaccines were administered according to package insert instructions during the first year of life; b routine toddler vaccines were: Prevnar and commercially available MMR/MMRV vaccine. Note: MMR/MMRV and rotavirus vaccines were not analysed for immunogenicity. When Prevnar 13 was administered, only the 7 pneumococcal antigens included in both vaccines were analysed for immunogenicity

Study V59_33 assessed the immunogenicity of 4-dose MenACWY series administered at 2, 4, 6, and 12 months of age, and the effect of co-administration of MenACWY on the immunogenicity of:

1. Routine infant vaccines (DTaP-IPV-Hib [Pentacel], Prevnar, and HBV [commercially available US-licensed vaccines]);
2. Routine toddler dose of Prevnar.

Overall, the study provides immunogenicity data to support a 2, 4, 6 and 12 months of age MenACWY schedule and data supporting concomitant use of MenACWY with routine infant/toddler vaccines currently recommended in the US.

7.2.2.2. Inclusion and exclusion criteria

As in 7.2.1.2.

7.2.2.3. Study treatments

Test vaccine was MenACWY as above and routine toddler vaccines were according to National Guidelines.

7.2.2.4. Efficacy variables and outcomes

The primary immunogenicity outcome was the sufficiency of the immune response following 4 doses of MenACWY vaccine given at 2, 4, 6 and 12 months in healthy infants in terms of the proportion of subjects with an hSBA \geq 1:8 at 1 month post vaccination, for each of the four meningococcal vaccine serogroups.

Secondary immunogenicity outcomes were:

- to evaluate the hSBA GMTs after 4 doses of MenACWY at 2, 4, 6 and 12 months against each of the four MenACWY serogroups
- the proportion of subjects with post vaccination hSBA $\geq 1:8$, fourfold rise, and hSBA GMTs after 3 doses of MenACWY at 2, 4, and 6 months against each of the four MenACWY serogroups
- to demonstrate that the immune responses to routine concomitant vaccinations (pneumococcal, IPV, HBV, Hib, DTaP) are non-inferior when given with MenACWY compared with when given without MenACWY. To assess the persistence of MenACWY immune responses at 12 months of age prior to the fourth dose.
- to evaluate the proportion of subjects with four-fold rise in hSBA at 1 month post 4th dose as compared to the pre 4th dose hSBA against each of the four MenACWY serogroups.

7.2.2.5. Randomisation and blinding methods

As in 7.2.1.5

7.2.2.6. Analysis populations

As in 7.2.1.6

7.2.2.7. Sample size

A total of 520 subjects (260 subjects per group) were planned to be enrolled in the study. A total of 529 subjects were enrolled and were randomised in a 1:1 ratio to receive either MenACWY concomitantly with routine vaccines (N=258) or routine vaccines alone (N=271). A total of 525 (255+270) subjects were analysed for safety, 411 (202+209) subjects were included in infant per protocol (PP) analysis and 352 (172+180) subjects were included in toddler PP analysis. Overall, 449 subjects from the US, 74 from Australia, and 6 from Canada were enrolled.

7.2.2.8. Statistical methods

The study was considered a success if the lower limit of the 95% CI for each serogroup met the levels as specified above and shown in Table 6.

7.2.2.9. Participant flow

A total of 529 subjects were enrolled in the study. Of the enrolled subjects, 414 (78%) subjects completed the study. Within the MenACWY immunogenicity PP populations, there were 411 (78%) subjects included after the 2, vaccination (toddler dose) to the end of the study (18 months of age) were similar between the vaccination groups (64% in Group 1 and 67% in Group 2).

7.2.2.10. Major protocol violations/deviations

These were most commonly blood draw or vaccination out of specified window, non-study concomitant vaccination given, and wrong or no vaccine given, inclusion/exclusion criteria violations. The number of subjects with major violations who were unable to continue in the study are summarised in Table 10.

Table 10: Study VP_33, Summary of Study Terminations

	Number (%) of Subjects		
	ACWY+R (Group 1)	Routine (Group 2)	Total
Enrolled (N)	258 (100%)	271 (100%)	529 (100%)
Completed study	213 (83%)	201 (74%)	414 (78%)
Premature withdrawals	45 (17%)	70 (26%)	115 (22%)
AE	2 (<1%)	5 (2%)	7 (1%)
Withdrew consent	16 (6%)	24 (9%)	40 (8%)
Lost to follow-up	15 (6%)	24 (9%)	39 (7%)
Inappropriate enrollment	2 (<1%)	0	2 (<1%)
Administrative reason	9 (3%)	15 (6%)	24 (5%)
Protocol deviation/violation	1 (<1%)	2 (<1%)	3 (<1%)

7.2.2.11. Baseline data

The demographic and other baseline characteristics were similar between subjects receiving MenACWY concomitantly with routine vaccines vaccination and those receiving only routine vaccinations.

7.2.2.12. Results for the primary efficacy outcome

One month post-MenACWY vaccination at 13 months of age (PP MenACWY toddler population), 89%, 95%, 97% and 96% of the subjects in Group 1 (ACWY+R) achieved hSBA \geq 1:8 against serogroups A, C, W and Y, respectively with the lower limit of the two-sided 95% CI (83%, 90%, 93% and 92%, respectively) being greater than 80%, 85%, 85% and 85% for MenA, MenC, MenW and MenY, respectively as shown in Table 7 and Table 11. Thus, the primary objective was met. The primary objective was also met after analysis in MITT population and in a subset of PP MenACWY toddler population with narrower acceptable window used for the blood draw.

Table 11: Study_33, Percentage of Subjects With hSBA \geq 1:8 at 1 Month After Toddler MenACWY Dose (4th Dose) - PP Toddler MenACWY Population

	Number (%) of Subjects (95% CI)							
	Men A		Men C		Men W		Men Y	
	ACWY+R (Group 1) N=168	Routine (Group 2) N=175	ACWY+R (Group 1) N=156	Routine (Group 2) N=171	ACWY+R (Group 1) N=153	Routine (Group 2) N=165	ACWY+R (Group 1) N=153	Routine (Group 2) N=159
Post-Toddler Dose	149 (89%) (83%-93%)	3 (2%) (0-5%)	148 (95%) (90%-98%)	4 (2%) (1%-6%)	149 (97%) (93%-99%)	11 (7%) (3%-12%)	147 (96%) (92%-99%)	2 (1%) (0-4%)

7.2.2.13. Results for other efficacy outcomes

In the PP MenACWY infant population, one month post-three dose infant series (at 7 months of age), 76%, 94%, 98% and 94% of the subjects in Group 1 achieved hSBA \geq 1:8 against serogroups A, C, W and Y, respectively. A total of 78%, 94%, 93% and 93% of the subjects in Group 1 had at least four-fold rise compared to the baseline blood draw at 2 months of age against serogroups A, C, W and Y, respectively. The hSBA GMTs in Group 1 increased over the baseline (A: 21, C: 74, W: 79, Y: 51) while those in Group 2 remained at the similar levels to baseline (Table 12).

Table 12: Results for Study V59_33, Immune Response 1 Month after Three Doses of Infant Series of MenACWY Vaccination - PP Infant MenACWY Population

	Number (%) of Subjects or GMTs (95% CI)							
	Men A		Men C		Men W		Men Y	
	ACWY+R (Group 1)	Routine (Group 2)	ACWY+R (Group 1)	Routine (Group 2)	ACWY+R (Group 1)	Routine (Group 2)	ACWY+R (Group 1)	Routine (Group 2)
hSBA $\geq 1:8$	N=202	N=208	N=199	N=206	N=194	N=202	N=188	N=196
Pre-infant series	3 (2%) (0-5) N=170	1 (1%) (0.014-3) N=178	11 (7%) (3-12) N=166	12 (7%) (4-12) N=174	20 (13%) (8-20) N=152	24 (15%) (10-21) N=164	11 (8%) (4-13) N=144	6 (4%) (1-9) N=150
Post-infant series	153 (76%) (69-81)	3 (1%) (0-4)	188 (94%) (90-97)	3 (1%) (0-4)	190 (98%) (95-99)	7 (3%) (1-7)	176 (94%) (89-97)	5 (3%) (1-6)
At Least 4-Fold Rise	N=170	N=177	N=164	N=171	N=147	N=158	N=135	N=142
Post-infant series	133 (78%) (71-84)	3 (2%) (0-5)	154 (94%) (89-97)	2 (1%) (0-4)	136 (93%) (87-96)	3 (2%) (0-5)	125 (93%) (87-96)	3 (2%) (0-6)
hSBA GMTs	N=202	N=208	N=199	N=206	N=194	N=202	N=188	N=196
Pre-infant series	2.09 (2.2-1.8) N=170	2.05 (1.98-2.12) N=178	2.49 (2.25-2.76) N=166	2.39 (2.18-2.61) N=174	2.94 (2.52-3.43) N=152	2.98 (2.58-3.45) N=164	2.52 (2.28-2.77) N=144	2.26 (2.12-2.41) N=150
Post-infant series	21 (17-26)	2.08 (1.99-2.17)	74 (62-87)	1.94 (1.64-2.3)	79 (67-92)	1.94 (1.68-2.24)	51 (43-61)	2.13 (2.02-2.25)

In the toddler MenACWY PP population, 89%, 92%, 95% and 96% of the subjects in Group 1 had at least a four-fold rise in hSBA against serogroups A, C, W and Y, respectively, from pre- to post-12 month hSBA. The hSBA GMTs in Group 1 increased considerably over the 2, 4, 6-month infant series GMTs (A: 54 versus 22, C: 135 versus 83, W: 215 versus 74; Y: 185 versus 48). At 12 months, 37%, 70% and 53% of the subjects in Group 1 had hSBA $\geq 1:8$ against serogroups C, W and Y, respectively. The hSBA GMTs in Group 1 were: 5.98 for serogroup C, 15 for serogroup W and 8.39 for serogroup Y while for serogroup A the hSBA GMTs were similar to GMT of non-vaccinated subjects. Table 8 shows that virtually all the non-inferiority criteria with other childhood vaccinations were met.

7.2.2.14. Evaluator commentary

The primary objective was met in terms of sufficiency of the immune response following 4 doses of MenACWY vaccine given at 2, 4, 6 and 12 months of age in healthy infants, which was demonstrated for each of the four meningococcal vaccine serogroups. This was shown one month post three-dose infant series (at 7 months of age) and also at 12 months of age. One month after the toddler dose (13 months of age), the hSBA GMTs in Group 1 were higher than after the infant series while those in Group 2 (Routine) remained low. One month after the toddler dose (at 13 months of age) 89%, 92%, 95% and 96% of the subjects in Group 1 had at least a four-fold rise in hSBA against serogroups A, C, W and Y, respectively, from pre- to post-12 month hSBA while no increase was observed in Group 2.

7.2.3. Study V59P21

7.2.3.1. Study design, objectives, locations and dates

This study was a Phase III, open label, randomised, multicentre study that concurrently enrolled 2 age groups of subjects, 7 to 9 months of age and 12 months of age. The study was conducted from February 2008 until October 2010 at 90 study sites in the US. A total of 1014 subjects 7 to 9 months of age were enrolled and randomised at a 1:1 ratio to receive (at 12 months of age) either MenACWY concomitantly with a measles, mumps, rubella, and varicella (MMRV) vaccine or MenACWY alone. Prior to the vaccination at 12 months of age, all 7- to 9-month-old subjects received MenACWY alone at the time of enrolment. The V59P21 study design is provided in Table 13.

Table 13: Study Design V59P21

Study Group	Months of Age			
	7 to 9 Months	8 to 10 Months	12 Months	13.5 Months
MenACWY+MMRV N=504	Enrollment MenACWY	N/A	Serology MenACWY MMRV	Serology
MenACWY N=510	Enrollment MenACWY	Serology	MenACWY	Serology MMRV
MMRV N=616	N/A	N/A	Enrollment Serology MMRV	Serology

The main objective of this study was to assess the immunogenicity of a 2-dose schedule of MenACWY administered to older infants, and the effect of co-administration of MenACWY on the immunogenicity of a routine toddler MMRV vaccine (ProQuad™, or MMRII™ and Varivax™) and vice versa (Table 14).

Table 14: Primary and Secondary Immunogenicity Endpoints for Assessing Non-interference of MenACWY on the MMRV Vaccine Administered at 12 Months of Age, Pivotal Study V59P21

Vaccine	Test	Antigens	Threshold	Endpoints
ProQuad or MMRII+Varivax	ELISA	<i>Measles Seroconversion</i>	≥ 255 mIU/mL	$\% \geq$ threshold
		<i>Mumps Seroconversion</i>	≥ 10 ELISA Ab units	$\% \geq$ threshold
		<i>Rubella Seroconversion</i>	≥ 10 IU/mL	$\% \geq$ threshold
		<i>Varicella Seroconversion</i>	≥ 5 gp ELISA units/mL	$\% \geq$ threshold
		Varicella Seroconversion	≥ 1.25 gp ELISA units/mL	$\% \geq$ threshold
		GMTs for measles, mumps, rubella, and varicella	N/A	GMT ratio

7.2.3.2. Inclusion and exclusion criteria

As in 7.2.1.2

7.2.3.3. Study treatments

MenACWY conjugate vaccine, as in 7.2.1.3.

ProQuad™ (Measles, Mumps, Rubella and Varicella vaccine; Merck & Co., Inc One 0.5 mL dose of ProQuad™ was administered SC in the anterolateral area of the left thigh. As an option, in case of the unavailability of ProQuad™, MMR™II and Varivax™ may have been administered.

7.2.3.4. Efficacy variables and outcomes

Immunogenicity

Primary:

- the percentage of initially seronegative subjects who show seroconversion for each of measles, mumps, rubella, and varicella.

Secondary:

- the geometric mean titres (GMTs) for antibodies to measles, mumps, rubella and varicella.

7.2.3.5. Randomisation and blinding methods

As in 7.2.1.5

7.2.3.6. Analysis populations

As in 7.2.1.6

7.2.3.7. Sample size

Approximately 1220 subjects aged 7 to 9 months (inclusive) at the time of enrolment were to be enrolled in the study and randomised in a 1:1 ratio to Group I or Group II. A total of 504 subjects were enrolled into Group I and 510 subjects were enrolled into Group II. In addition, 610 subjects aged 12 months (inclusive) at the time of enrolment were to be enrolled in an open label arm in vaccination Group III. There were 616 subjects enrolled into Group III.

7.2.3.8. Statistical methods

The immunogenicity measures of MenACWY, for each serogroup, are described above (Table 6). These were considered to be non-inferior to the immunogenicity of MMRV administered alone if the lower limit of the two-sided 95% CI of the difference in the percentage of subjects with seroconversion for measles, mumps and rubella and seroprotection for varicella at 6 weeks after MMRV vaccination {PMMRV + MenACWY minus PMMRV} was greater than -5% for measles, mumps and rubella and was greater than -10% for varicella (Group I versus Group III).

The immune response of MenACWY given concomitantly with MMRV (Group I) was to be considered non-inferior to the immunogenicity of MenACWY administered alone (Group II) if the lower limit of the two-sided 95% CI around the difference of the percentage of subjects with hSBA \geq 1:8 at 6 weeks after the second dose of MenACWY given to 12-month old toddlers {PMMRV + MenACWY minus PMenACWY} was greater than -10% for each serogroup (Group I versus Group II at Visit 4).

The primary criteria for the immunogenicity of two doses of MenACWY given to young children at 7 to 9 and 12 months of age (Group II) was that the lower limit of the two-sided 95% confidence interval for the percentage of subjects with hSBA \geq 1:8 at 6 weeks after MenACWY was at least 85% for serogroups C, W-135, or Y and at least 65% for serogroup A.

7.2.3.9. Participant flow

A total of 1630 subjects were enrolled and randomised (504 in Group I [MenACWY + MMRV], 510 in Group II [MenACWY] and 616 in Group III [MMRV]), while 1603 subjects were vaccinated (500 in MenACWY + MMRV group, 503 in the MenACWY group and 600 in the MMRV group). A total of 225 subjects withdrew prematurely from the study, while 1405 completed the study as per protocol. Of the 225 subjects who withdrew prematurely, 78 were in the MenACWY + MMRV group, 88 were in the MenACWY group and 59 were in the MMRV group. Across all groups, premature withdrawals were due to withdrawal of consent (80 subjects), lost to follow-up (68 subjects), protocol deviation/violation (56 subjects), inappropriate enrolment (12 subjects), administrative reason (8 subjects), and AE (1 subject).

7.2.3.10. Major protocol violations/deviations

In total 867 subjects had protocol deviations during the conduct of the study: 286 [57%] in the MenACWY + MMRV group, 354 [69%] in the MenACWY group and 227 [37%] in the MMRV group; Table 14.1.1.8). Major protocol deviations were recorded in 365 subjects: 139 [28%] in the MenACWY + MMRV group, 133 [26%] in the MenACWY group and 93 [15%] in the MMRV group). Differences in the number of protocol deviations were related to different study procedures and number of visits for the different groups. The most frequent major deviations were, by decreasing order: no blood draws, no MMRV immunisation, no MenACWY immunisation, sample available but no ACWY serology results, subjects received excluded concomitant treatment or vaccine.

7.2.3.11. Baseline data

Demographic and other baseline characteristics of the overall randomised population were similar across all groups. The majority of the population was Caucasian. The ratios between males and females were similar across all groups. The mean age was 8.5 ± 0.8 months in the MenACWY + MMRV and MenACWY groups where the first vaccination was at 7 to 9 months of age and it was 12.1 ± 0.3 months in the MMRV group where the first vaccination was at 12 months of age. Weight and height were similar between MenACWY + MMRV and MenACWY groups, and were greater in MMRV group where the children were older.

7.2.3.12. Results for the primary efficacy outcome

Analyses of MMRV immunogenicity

Observed seroconversion rates were slightly higher (by 1-2%) in the MMRV group compared to the MenACWY + MMRV group for measles (99% versus 98%) and rubella (97% versus 95%). The observed seroconversion rate was slightly lower by 2% for mumps (96% versus 98%). The observed seroprotection rate was higher in the MMRV group compared to the MenACWY + MMRV group for Varicella (98% versus 96%). The lower limit of the two-sided 95% CI for the difference between the percentage of subjects with seroconversion in the MenACWY + MMRV group and the percentage of subjects with seroconversion in the MMRV group was -3.4%, -1.0%, and -4.5% for measles, mumps, and rubella, respectively. The lower limit of the two-sided 95% CI for the difference between the percentage of subjects with seroprotection against varicella in the MenACWY + MMRV group and the MMRV group was -3.9%. These results satisfied the protocol-specified non-inferiority criterion for each of these four antigens

7.2.3.13. Results for other efficacy outcomes

Analyses of MenACWY immunogenicity

The lower limits of the two-sided 95% CI for the difference between the percentage of subjects with hSBA $\geq 1:8$ in MenACWY + MMRV group and the percentage of subjects with hSBA $\geq 1:8$ in the MenACWY group at 6 weeks after the second dose of MenACWY at 12 months of age was -4.7%, -1.8%, -1.3%, and -1.9% for serogroups A, C, W-135, and Y, respectively. These results satisfied the protocol-specified non-inferiority criterion for each of these four serogroups.

Also in the MenACWY group, after 2 doses, the lower limit of the two-sided 95% CI is for the percentage of subjects with hSBA $\geq 1:8$ were 98%, 96%, and 93% for serogroups C, W-135, and Y, respectively. The lower limit of the two-sided 95% CIs was 84% for serogroup A. The results show that pre-specified criteria for 'adequate immune response' were met for the two-dose MenACWY schedule in older infants. GMTs after two doses of MenACWY (assessed 6 weeks post dose 2 at Visit 4) given with MMRV were 39, 194, 132, and 97 in serogroups A, C, W-135, and Y, respectively. These were shown to be non-inferior to the GMTs in the subjects who only received MenACWY alone for all four serogroups.

7.2.3.14. Evaluator commentary

The primary objectives of this Phase III study were to assess the safety and immune response elicited by the concomitant administration of MMRV, given as ProQuad™ with MenACWY when given to healthy toddlers. The results support the concomitant use of the vaccines. The study was complicated by a supply interruption of ProQuad™ where the component vaccines, M-M-R™II and Varivax™, were substituted. Analysis of comparability of the component vaccine and ProQuad™ supported the pooling of the data from these groups into a single group designated MMRV (it also reflects a real life situation better, in which children are given different vaccines). All primary immunogenicity objectives were met. Concomitant administration of MMRV with MenACWY did not affect the immune response to MenACWY for any of the serogroups. The immune response to MenACWY administered concomitantly with MMRV was non-inferior to the response to MenACWY alone as measured by the percentage of subjects with hSBA $\geq 1:8$.

7.2.4. Study v59P20

7.2.4.1. Study design, objectives, locations and dates

This was a Phase III, randomised, observer-blind, multicentre study conducted in the US and Canada in children 2-10 years of age to compare the safety and immunogenicity of MenACWY with Menactra. Enrolment included 1278 single-dose MenACWY subjects, 1270 single-dose Menactra subjects, and 539 2-dose MenACWY subjects. This was conducted between March 2008 and October 2009. A total of 2907 healthy children 2 to 10 years of age were randomly assigned to either MenACWY or Menactra. The randomisation was stratified by age with the following per age strata: children 2 to 5 years of age (n = 1751), and children 6 to 10 years of age (n = 1156). In the 2 to 5 years of age group, subjects were randomised in a 1:2:2 ratio to receive either 2 doses of MenACWY, one dose of MenACWY, or one dose of Menactra. The subjects age 6 to 10 were randomised in a 1:1 ratio to receive a single dose of either MenACWY or Menactra.

The primary objectives were to compare the immunogenicity of a single dose of MenACWY with the immunogenicity of a single dose of Menactra, defined as the percentage of subjects with seroresponse directed against *N. meningitidis* serogroups A, C, W, and Y, at 1 month post-vaccination, when administered to children 2-5 years of age and also to children 6-10 years of age.

Secondary objectives

- To assess the immunogenicity of two doses of MenACWY, administered 2 months apart, and compare it to the immunogenicity of a single dose of MenACWY, defined as percentage of subjects with seroresponse, hSBA \geq 1:4, hSBA \geq 1:8 and hSBA GMTs directed against *N. meningitidis* serogroups A, C, W-135, and Y, at 1 month after vaccination, when administered to healthy children 2 to 5 years of age.
- To compare the immunogenicity of a single dose of MenACWY with the immunogenicity of a single dose of Menactra, defined as percentage of subjects with hSBA \geq 1:4, hSBA \geq 1:8, and hSBA GMT response directed against *N. meningitidis* serogroups A, C, W-135, and Y, at 1 month after vaccination, when administered to healthy subjects 2 to 5 years of age or 6 to 10 years of age.

7.2.4.2. Inclusion and exclusion criteria

As in 7.2.1.2 (with relevant age criteria).

7.2.4.3. Study treatments

The test product was MenACWY as in the other studies.

Licensed meningococcal ACWY polysaccharide-protein conjugate vaccine Menactra (manufactured by Aventis Pasteur Inc.) was supplied as a single 0.5 mL injection (administered by IM injection in the left deltoid area) formulated in sodium phosphate buffered isotonic sodium chloride solution to contain 4 µg each of meningococcal A, C, Y, and W-135 polysaccharides conjugated to approximately 48 µg of diphtheria toxoid protein carrier.

7.2.4.4. Efficacy variables and outcomes

In terms of immunogenicity, the success criteria for this study was based upon the primary objective for the per protocol population, that is, for both age strata, all four serogroup analyses met the non-inferiority criteria identified for the endpoint noted above. The secondary outcomes are also described above.

7.2.4.5. Randomisation and blinding methods

Randomisation as in 7.2.1.5. Observers were blinded as to which vaccine subjects had received.

7.2.4.6. Analysis populations

As in 7.2.1.6

7.2.4.7. Sample size

Approximately 2820 subjects 2 to 10 years of age were planned to be randomly assigned to receive either two doses of MenACWY, a single dose of MenACWY, or a single dose of Menactra. The randomisation was stratified by study site and age group (2-5 Years, 6-10 Years). In total, 2907 subjects were enrolled and 2802 subjects completed the study.

7.2.4.8. Statistical methods*Primary*

For each age group (2 to 5 Years and 6 to 10 Years), immunogenicity of MenACWY was considered non-inferior to the immunogenicity of Menactra, for any of the four serogroups, if the lower limit of the two-sided 95% CI around the difference in the percentage of subjects with seroresponse for that serogroup (MenACWY minus Menactra) was greater than -10%. If the CI is entirely to the right of -10%, then non-inferiority was declared for that serogroup. Moreover, if the CI was entirely to the right of 0%, then MenACWY was considered to have met criteria for statistical superiority for the immune response compared to Menactra for that serogroup. The combined hypothesis testing for non-inferiority and statistical superiority did not require any adjustment for multiplicity.

Secondary

Immunogenicity of MenACWY was considered non-inferior to the immunogenicity of Menactra, for any of the four serogroups, if the lower limit of the two-sided 95% CI around the difference of the percentage of subjects with hSBA $\geq 1:8$ (or hSBA $\geq 1:4$) for that serogroup (MenACWY minus Menactra) was greater than -10%. Using GMTs, the immune response of MenACWY would be considered non-inferior to the immunogenicity of Menactra, in the 2 to 10 years group or each age stratum separately, if the lower limit of the two-sided 95% confidence interval (CI) around the ratio of hSBA GMTs between MenACWY and Menactra, 1 month after vaccination, was greater than 0.5.

7.2.4.9. Participant flow

A total of 2907 subjects were enrolled and randomised to receive either 2 doses of MenACWY, a single dose of MenACWY, or a single dose of Menactra. A total of 359 subjects were randomised to receive 2 doses of MenACWY, 1278 were randomised to receive a single dose of MenACWY, and 1270 were randomised to receive a single dose of Menactra. The PP population for subjects who received 2 doses of MenACWY, or a single dose of MenACWY or Menactra was approximately 83%, 92% and 91%, respectively, of the randomised populations. This is shown in Table 15.

Table 15: Study V59P20, participant flow

Vaccine Group	Subjects enrolled (planned) and actual	Subjects enrolled (planned) and actual	
		2-5	6-10
MenACWY 2-Doses	(340) 359	(340) 359	N/A
MenACWY	(1240) 1278	(680) 696	(560) 582
Menactra	(1240) 1270	(680) 696	(560) 574

7.2.4.10. Major protocol violations/deviations

In total 646 subjects had protocol deviations during the conduct of the study (144 [40%] in the MenACWY 2-dose group, 258 [20%] in the MenACWY group and 244 [19%] in the Menactra group). A total of 279 subjects had major protocol deviations. The rate of observed deviations was similar between groups (MenACWY and Menactra). The major protocol deviations were higher in the MenACWY 2-dose group than MenACWY single dose group. 2 to 5 year olds also reported more major protocol deviations than 6 to 10 year olds most likely because of the more complex visit/dosing in 2-5 year old group or difficulty in drawing blood from the younger subjects. The subjects with major protocol deviations were excluded from the immunogenicity analyses. The most common deviation among the major protocol deviation was 'No post-vaccination blood draw, followed by 'No pre-vaccination blood draw' and then 'Post-vaccination blood draw-out of window'.

7.2.4.11. Baseline data

Demographic and other baseline characteristics of the overall randomised population (2 to 10 years of age) were similar in the MenACWY 2-dose, MenACWY and Menactra groups (Table 16). The majority of the population was Caucasian. The ratios between males and females were similar across all the vaccine groups. Other baseline characteristics were well balanced between comparator groups (that is, MenACWY versus Menactra in the 2-5 or 6-10 strata, or 2 doses of MenACWY versus 1 dose among subjects 2- 5 years of age).

Table 16: Study V59P20, Percentage of Subjects with hSBA Seroresponse at 1 Month Post vaccination (95% CI) by Age Group, PP Population

Sero-group		2-5 Years			6-10 Years		
		MenACWY	Menactra	Vaccine Group Difference MenACWY - Menactra	MenACWY	Menactra	Vaccine Group Difference MenACWY - Menactra
A	Baseline	424 (72%)	461 (77%)	-6%	411 (77%)	438 (83%)	-6%
	hSBA < 1:4	(68-75) N=591	(74-81) N=596	(-11--1)	(73-80) N=535	(80-86) N=526	(-11--2)
	Baseline	10 (67%)	8 (53%)	13%	11 (69%)	9 (60%)	9%
	hSBA ≥ 1:4	(38-88) N=15	(27-79) N=15	(-21-45)	(41-89) N=16	(32-84) N=15	(-24-40)
	Overall	434 (72%) (68-75) N=606	469 (77%) (73-80) N=611	-5% (-10-0)	422 (77%) (73-80) N=551	447 (83%) (79-86) N=541	-6% (-11--1)
C	Baseline	306 (62%)	294 (58%)	4%	231 (67%)	209 (63%)	4%
	hSBA < 1:4	(58-67) N=491	(54-63) N=503	(-2-10)	(61-72) N=347	(57-68) N=334	(-3-11)
	Baseline	57 (49%)	52 (46%)	3%	118 (57%)	100 (49%)	8%
	hSBA ≥ 1:4	(40-59) N=116	(37-56) N=112	(-10-16)	(50-64) N=207	(42-56) N=205	(-1-18)
	Overall	363 (60%) (56-64) N=607	346 (56%) (52-60) N=615	4% (-2-9)	349 (63%) (59-67) N=554	309 (57%) (53-62) N=539	6% (0-11)
W	Baseline	383 (87%)	321 (68%)	18%	239 (84%)	210 (71%)	12%
	hSBA < 1:4	(83-90) N=442	(64-73) N=469	(13-23)	(79-88) N=285	(66-77) N=294	(6-19)
	Baseline	43 (28%)	28 (21%)	8%	69 (27%)	26 (11%)	16%
	hSBA ≥ 1:4	(21-36) N=152	(14-28) N=136	(-2-17)	(22-33) N=257	(7-16) N=239	(9-23)
	Overall	426 (72%) (68-75) N=594	349 (58%) (54-62) N=605	14% (9-19)	308 (57%) (53-61) N=542	236 (44%) (40-49) N=533	13% (7-18)
Y	Baseline	352 (72%)	246 (50%)	22%	241 (70%)	169 (49%)	21%
	hSBA < 1:4	(67-75) N=492	(45-54) N=496	(16-28)	(65-75) N=344	(43-54) N=347	(14-28)
	Baseline	42 (42%)	25 (24%)	18%	75 (37%)	43 (22%)	15%
	hSBA ≥ 1:4	(32-52) N=101	(16-33) N=104	(5-30)	(31-44) N=201	(17-29) N=192	(6-24)
	Overall	394 (66%) (62-70) N=593	271 (45%) (41-49) N=600	21% (16-27)	316 (58%) (54-62) N=545	212 (39%) (35-44) N=539	19% (13-24)

7.2.4.12. Results for the primary efficacy outcome

In the 2-10 year population of this study, the immune response as measured by seroresponse one month post-vaccination was statistically superior for MenACWY when compared to Menactra for serogroups C, W, and Y, and non-inferior for serogroup A. As measured by hSBA $\geq 1:8$, MenACWY was statistically superior to Menactra for serogroups W and Y, and non-inferior for A and C. The immune response as measured by hSBA GMTs was statistically significantly higher for MenACWY than for Menactra for serogroups C, W, and Y, and non-inferior for serogroup A.

7.2.4.13. Results for other efficacy outcomes

For subjects 2-10 years, in the comparison of one dose of MenACWY versus one dose of Menactra, the proportion of subjects with seroresponse and with a post vaccination hSBA $\geq 1:8$ was non-inferior for all four serogroups. Moreover, MenACWY met the criteria for statistical superiority compared to Menactra for serogroups C, W and Y for the proportion of subjects with seroresponse and for serogroups W and Y for the proportion of subjects with post vaccination hSBA $\geq 1:8$. Similarly, for subjects 2-10 years, the GMTs following one dose of MenACWY were non-inferior to Menactra for all four serogroups. Among subjects aged 2-5 years, for all endpoints tested (percentage of subjects with seroresponse, hSBA $\geq 1:8$ and hSBA GMTs), subjects who received two doses of MenACWY had significantly higher immune response than subjects who received only one dose of MenACWY.

For both the 2-5 and 6-10 years of age subgroups, the immune response as measured by seroresponse (primary objective) and by the percentage of subjects with hSBA $\geq 1:8$ was similar for each vaccine group (Table 16). MenACWY was shown to have a statistically superior seroresponse than Menactra for serogroups W and Y, and a non-inferior seroresponse for serogroup C but did not meet the non-inferiority criterion for serogroup A. Furthermore, the immune response as measured by GMTs showed that MenACWY was statistically significantly higher than Menactra for serogroups C, W, and Y, and was non-inferior to Menactra for serogroup A for both age groups. Although non-inferiority was not achieved for serogroup A within the age subgroups, it was when they were combined.

7.2.4.14. Evaluator commentary

This was a well conducted study which found that the immune response to one dose of MenACWY was non-inferior to one dose of Menactra for serogroups C, W and Y and statistically superior for serogroups W and Y, for children aged 2-5 and 6-10. Although non-inferiority was not met for seroresponse to serogroup A within the age groups, point estimates of GMTs were higher for MenACWY than Menactra and non-inferiority achieved.

7.3. Other efficacy studies

7.3.1. Study V59P5

This supportive study was a Phase II, randomised, open-label, controlled multicentre study to evaluate safety, immunogenicity, and induction of immunological memory after multiple doses of MenACWY (adjuvanted and unadjuvanted formulations). The study enrolled healthy infants 2 months of age (55 to 89 days inclusive) and was conducted in Canada and in the UK from September 2004 until October 2006. Overall, a total of 601 infants were enrolled into the study, including 286 subjects from Canada and 315 subjects from the UK (Table 17). Only data for the 180 subjects enrolled to receive the final, unadjuvanted MenACWY formulation (2 of the total 7 study groups) are pertinent to this submission.

Table 17: Supportive efficacy and safety studies

Study	MenACWY Vaccination Schedules (Months of Age) ^a	Objectives of the Study	Study Design and Type of Control	Test Products ^b (Vaccination Schedules – Months of Age)	Number of Subjects Enrolled	Subjects' Ages at Enrolment; Geographic Location
V59P5 ^c	2, 4, 12	MenACWY: immunogenicity, memory, persistence	Randomized open-label, controlled, multicenter	MenACWY (2,4,12)	135	2 months; UK, Canada
				MenACWY (2, 4) followed by 1/5 Menomune (12)	45	
				MenACWY Ad+ (2, 4 or 2,4,6) followed by 1/5 Menomune (12)	98	
				MenACWY Ad+ (2,3,4,12 or 2,4,12 or 2, 4, 6)	278	
				Menjugate (2,4) followed by MenACWY+ (12)	45	
V59P7	1 st dose 12 to 24 2 nd dose: 1, 6 or 12 mos after 1 st dose	MenACWY: 1 vs. 2 doses, effect on immunogenicity of different spacing of doses	Randomized, controlled, observer-blind, multicenter	MenACWY (all schedules)	114 (220 ^d)	1-5 years ^e Finland, Poland
				MenACWY Ad+ (all schedules)	108 (99 ^d)	
				Mencevax ⁴	0 (82 ^d)	
V59P8	12 to 15 16 to 23	MenACWY: immunogenicity and safety	Randomized, controlled, single-blind, single-center	MenACWY (12-15)	74	1-10 years ^f , US
				MenACWY+PnC (12-15)	73	
				MenACWY (16-23)	71	
				MenACWY+DTaP (16-23)	73	
V59P9 ^c	6, 12 or 12	MenACWY: immunogenicity of 1 vs. 2 doses	Open label, partially randomized, multicenter	MenACWY (6, 12)	64	6-12 months Canada
				MenACWY (12)	61	
				Menjugate (12) followed by MenACWY (18)	50	

Immunogenicity assessments: This study assessed the immunogenicity of multiple dose schedules of MenACWY administered to healthy infants/toddlers. The study groups relevant to this submission (that is, those that received the final vaccine formulation) followed a MenACWY vaccination schedule at 2, 4, and 12 months of age. However, only immunogenicity data obtained after the doses administered at 2 and 4 months of age are submitted as relevant for this application they provide data on antibody responses that may be observed at an earlier time point within the proposed 4-dose infant. Safety assessments similar to all the other studies were made.

7.3.1.1. Results

The null hypothesis for the primary objective of the study was rejected based on the finding that the lower limit of the two-sided 95% CI of the percentage of subjects with hSBA titres $\geq 1:4$ exceeded the criterion 70% for MenACWY three-dose Ad+ regimens (vaccinations at 2, 3, and 4 months [93% to 97% in UK infants] and at 2, 4, and 6 months [81% to 99% in Canadian infants] of age) against at least one serogroup (the criterion 70% was met by both three-dose vaccine groups against all four serogroups). These findings supported the conclusion that both three-dose MenACWY Ad+ regimens were highly immunogenic against all four serogroups in UK and Canadian subjects during the study. Secondary analyses showed that similar results were

obtained in percentage of subjects with hSBA titres $\geq 1:8$ and in GMTs, except against the A serogroup. Although a significant percentage of subjects had hSBA $\geq 1:4$ at study entry, the data suggested that the source of this antibody was likely maternal, as subjects who received Menjugate had negative titres for W and Y serogroups at 5 months of age suggesting the natural decay of passively transferred antibodies.

Additional secondary analyses showed that two-dose MenACWY Ad+ and Ad- vaccines were immunogenic against all four serogroups, and there were no significant differences between UK Ad+ and Ad- groups and between Canadian Ad+ and Ad- groups. GMT and GMR results were similar to 1:4 and 1:8 results, except in the following instances: (a) GMTs were significantly higher in the Ad+ group than in the Ad- group in the UK against both the A and W serogroups, (b) GMTs were significantly lower in the Canadian Ad+ group than in the Ad- group against both the W and Y serogroups. Percentages of subjects with hSBA titres $\geq 1:4$ and $\geq 1:8$, and GMTs and GMRs were generally substantially less against the A serogroup than against C, W, and Y serogroups. The immunogenicity of routine vaccines administered concomitantly with MenACWY Ad+ and Ad- vaccines, such as Pediacel in the UK and Pentacel, HBV and Prevnar in Canada, resulted in expected response, as measured by titres against H influenza serotype b (Hib), diphtheria, tetanus, Pneumococcus, and hepatitis B.

7.3.2. Study V59P7

This was a Phase II, randomised, observer-blind, multicentre, active controlled study to evaluate safety and immunogenicity of MenACWY (adjuvanted and unadjuvanted formulations) in toddlers and children 12 months to 5 years of age (Table 17). This was a four arm study that examined the immunogenicity of MenACWY with (Ad+) and without (Ad-) adjuvant after a single injection and after a booster dose administered within a year of the first dose. In addition, within the subset of older children aged 36-59 months, the study assessed the immune response to a single dose of MenACWY Ad- and MenACWY PS (Mencevax), and the response in these subjects to a booster dose with MenACWY Ad- (the MenACWY PS recipients did not receive a booster dose with the polysaccharide vaccine). The study was conducted in Finland and Poland from March 2005 to May 2006. The overall study population was stratified by age, as follows:

- (i) Subjects 12 to 35 months of age (further stratified into subjects 12 to 24 and subjects 25 to 35 months of age); and
- (ii) Children 3 to 5 years of age.

Overall, Study V59P7 enrolled a total of 623 children, 114 of whom were 12 to 24 months of age and received the final, unadjuvanted MenACWY formulation. A total of 228 subjects 2-5 years of age were randomised to receive MenACWY and 82 subjects 3-5 years of age were randomised to receive Mencevax.

Immunogenicity assessments: this study assessed the immunogenicity of a 2-dose catch-up series of the final MenACWY formulation in toddlers and children. The effect of different intervals between the first and the second dose on the overall immune response to the series was assessed. The following vaccination schedules were explored: first dose administered at 12 to 24 months of age, followed by a second dose administered either 1, 6, or 12 months after the first dose. Safety assessments were done but only immunogenicity data from this study (supportive data for the 2-dose catch-up schedule in toddlers) are presented is included in this submission.

7.3.2.1. Results

A total of 623 subjects were enrolled in this study. One hundred eighty two (182) of the 210 children aged 36 to 59 months randomised to MenACWY Ad- (101 subjects) or MenACWY PS vaccine (81 subjects) were included in the PP population of the first vaccination; 161 of the 194 children, who received the second vaccination with MenACWY Ad- 6 or 12 months later (93 in the MenACWY Ad- and 68 in the MenACWY PS group) were included in the PP population of the second vaccination. Overall, the PP population comprised 92% of the enrolled population.

Baseline and other demographic characteristics were generally balanced between the vaccine groups. Vaccination with MenACWY Ad+ or MenACWY Ad- resulted in similar immune responses in toddlers 12 to 35 months of age, although the GMR for serogroups A and C were slightly higher in the MenACWY Ad+ group compared to the MenACWY Ad- group. At 1 month post-vaccination, hSBA GMTs for all four serogroups increased in both vaccine groups, and were similar or higher in the MenACWY than in the Mencevax group (serogroup A: 14 versus 6.93; serogroup C: 6.63 versus 7.46; serogroup W: 20 versus 12; serogroup Y: 17 versus 15). The second vaccination with MenACWY Ad- showed robust immune responses with the highest responses observed in subjects administered the second dose 12 months after the first. Except for serogroup A, hSBA persisted in a high proportion of subjects at 6 or 12 months after the first vaccination. Following two doses of MenACWY Ad- in toddlers, hSBA persisted in the majority of subjects at 1 year post first dose for serogroups C, W, and Y.

7.3.3. Study V59P9

This was a Phase II, partially randomised, open-label multicentre study primarily designed to evaluate a 2-dose MenACWY series administered at 6 and 12 months of age. The study was conducted in Canada from June 2005 to November 2006. The study enrolled:

- (i) Healthy infants 6 months of age; and
- (ii) Toddlers 12 months of age.

The 2 study populations differed both in terms of vaccines received and vaccination schedules applied. Overall, a total of 175 subjects were enrolled, including 125 infants (pertinent to this dossier) and 50 toddlers. Of the 3 study groups included in the overall study design, two, pertinent to this dossier, enrolled healthy 6-month-old infants who were administered either MenACWY at 6 and 12 months of age or a single dose of MenACWY at 12 months of age. Routine paediatric vaccines, as per Canadian vaccination schedule, were administered to all subjects, including concomitantly administered Pentacel and Prevnar at 6 months of age and toddler Prevnar at 12 months of age. Immunogenicity assessments: this study assessed the immunogenicity of a 2-dose catch-up series of MenACWY administered at 6 and 12 months of age versus the immunogenicity of a single dose of MenACWY administered at 12 months of age. Safety assessments were the same as in the previously described studies.

7.3.3.1. Results

Primary analyses of the two-dose MenACWY group ACWY 6-12m (Group I): In the ACWY 6- to 12-month vaccine group (Group I), the persistence of hSBA after the first vaccination of MenACWY (Visit 1) was still apparent before the second vaccination at 12 months of age (visit 3) against C, W, and Y (85%, 85%, and 72%), but not A (10%), serogroups. In the primary analysis, after the second MenACWY vaccination at 12 months of age in the ACWY 6-12m group, the percentages of subjects with hSBA titres of 1:4 or greater showed that two vaccinations with MenACWY at 6 and 12 months of age were highly immunogenic (88%, 100%, 100%, and 100% against A, C, W, and Y serogroups, respectively).

Secondary analyses of the two-dose MenACWY group ACWY 6-12m (Group I): Confirming the primary analysis, GMTs for the ACWY 6- to 12-month group were significantly elevated after two vaccinations of MenACWY 6 months apart against all four serogroups (44, 302, 220, and 136 against A, C, W, and Y serogroups, respectively). GMRs ranged from 15- to 18-fold increases in GMTs against the four serogroups at 12 months of age compared to those at 6 months of age. Percentages of subjects with hSBA titres of 1:8 or greater (84%, 100%, 100%, and 100% against A, C, W, and Y serogroups, respectively) further supported the conclusion that two vaccinations of MenACWY 6 months apart produced highly immunogenic results against all four serogroups and that the 1:8 results were very similar to results obtained using the 1:4 threshold.

Secondary analyses of the one-dose MenACWY group ACWY 12m: GMTs after one vaccination of MenACWY at 12 months increased against all four serogroups (11, 40, 30, and 10 against A, C, W, and Y, respectively) but were lower than the ACWY 6-12m two dose, indicating that the

ACWY 6-12m two-vaccination group was more highly immunogenic than the one-vaccination ACWY 12m group. GMRs in the ACWY 12-month vaccine group ranged from 5.17 to 20-fold increases against the four serogroups. Percentages of subjects with hSBA titres of 1:8 or greater (60%, 93%, 93%, and 67% against A, C, W, and Y serogroups, respectively) were very similar to results obtained for the 1:4 threshold and less than the ACWY 6-12m two-dose group for all serogroups.

Secondary analyses of MenC against the C serogroup: MenC with concomitant Pevnar at 12 months of age (C12 ACWY18 group) induced significant increases in GMTs against serogroup C at 13 months of age. The mean GMT at 13 months of age was 19-fold above the mean GMT before vaccination at 12 months of age (Visit 1). Percentages of subjects with hSBA of 1:4 and 1:8 or greater showed that MenC with concomitant Pevnar at 12 months of age was highly immunogenic 1 month later (93% and 88%, respectively).

Secondary analyses of MenACWY and concomitant Pentacel against A, W, and Y serogroups: MenC and concomitant Pevnar vaccination at 12 (group C12 ACWY18) months produced an immunogenic effect before injections at 18 months against the C serogroup. One month after vaccinations at 19 months of age, GMTs (8.05, 17, and 13) and percentages of subjects with hSBA of 1:4 or greater (63%, 81%, and 79%) and of 1:8 or greater (50%, 76%, and 63%) showed significant immunogenicity against A, W, and Y serogroups, respectively.

Secondary analyses of the booster response of the C component of MenACWY: Group C12 ACWY18 subjects who received a single injection of MenC with concomitant Pevnar at 12 months of age exhibited significant increases in GMT against serogroup C at 13 months of age (visit 2 GMT = 39, GMR = 19) and percentages of subjects with hSBA of 1:4 or greater (93%) and 1:8 or greater (88%). Group C12 ACWY18 results obtained at Visit 3 and Visit 4 showed that a MenACWY booster effect against serogroup C at 19 months of age was highly immunogenic and was greater than the original persistence effect at 13 months of age. Before a single vaccination of MenACWY at 18 months of age, the C12 ACWY18 vaccine group continued to exhibit significant elevation in GMT against serogroup C (visit 3 GMT = 29) and in the percentage of subjects who achieved the 1:4 or greater threshold (89%) and the 1:8 or greater threshold (82%). One month later at 19 months of age (1 month after MenACWY vaccination), GMT was 667, GMR was 23, percentage of subjects with hSBA of 1:4 or greater was 100%, and percentage of subjects with hSBA of 1:8 or greater was 100%.

7.3.4. Evaluator commentary: other efficacy studies

These were all well conducted Phase II studies. The Study V59P5 sub-groups submitted with this application found that immunogenicity was similar both with and without adjuvanted vaccine, also that the percentages of subjects with hSBA titres \geq 1:4 and \geq 1:8, and GMTs and GMRs were generally substantially less against the A serogroup than against C, W, and Y serogroups. The immunogenicity of routine vaccines administered concomitantly with MenACWY Ad+ and Ad- vaccines was not affected with MenACWY. In Study V59P7, the two dose catch up series showed adequate immunogenicity in toddlers and children, with the highest responses observed in subjects with the second dose administered 12 months after the first. Responses (except for serogroup A) persisted in a high proportion of subjects at 6 or 12 months after the first vaccination. Following two doses of MenACWY Ad- in toddlers, hSBA persisted in the majority of subjects at 1 year post first dose for serogroups C, W, and Y. In Study V59P9, overall, the study provided immunogenicity data to support a 2-dose catch-up schedule for older infants, once again with the lowest response to serogroup A.

7.4. Analyses performed across trials: pooled and meta-analyses

Overview is on the data from the 3 pivotal studies, organized as outlined below:

- Adequacy of the immune response elicited by the proposed 4-dose MenACWY series (pivotal Studies V59P14 and V59_33);
- Non-interference between routine infant/toddler vaccines and the proposed MenACWY series (pivotal Studies V59P14, V59_33, and V59P21);
- Adequacy of the immune response elicited by the proposed 2-dose catch-up MenACWY series (pivotal Studies V59P21 and V59P14 and supportive Studies V59P7 and V59P9);
- Evidence of the ability of MenACWY to induce immunologic memory (pivotal Studies V59P14 and V59_33 and supportive Study V59P9,

Data from the pivotal Studies V59P14 and V59_33, found that at 1 month after the 4-dose series administered at 2, 4, 6, and 12 or 16 months of age, the point estimate percentages of subjects with hSBA \geq 1:8 observed across the 3 cohorts of Studies V59P14 and V59_33 ranged from 89% to 95% for serogroup A and from 95% to 100% for serogroups C, W, and Y (Table 7). The LL of the 95% CI around the percentage of subjects with hSBA \geq 1:8 observed at 1 month after the fourth dose ranged between 83% and 89% for serogroup A and between 90% and 97% for serogroups C, W, and Y, comfortably meeting the criteria for demonstrating adequacy of the immune response to the 4-dose series pre-specified in Studies V59_33 and V59P14. The conclusion that there is an adequate immune response to the proposed 4-dose MenACWY series in infants/toddlers (the first 3 doses administered at 2, 4, and 6 months of age, with the fourth dose administered in the second year of life) is supported by an overall dataset from 3 Phase III, separately enrolled cohorts across Studies V59P14 (US and LA cohorts) and V59_33. Overall, this dataset consisted of 386 infants included in the PP populations of the 2 studies who had an available result for at least one serogroup. Even after the first 3 doses of MenACWY, that is, after the infant series at 2, 4, and 6 months of age, high percentages of subjects achieved hSBA \geq 1:8. The point estimates observed across Studies V59P14 and V59_33 ranged between 67% and 89% for serogroup A and between 94% and 98% for serogroups C, W, and Y. If the post-dose 4 criteria pre-specified in Studies V59_33 and V59P14 (that is, LL of the 95% > 80% for serogroup A and > 85% for serogroups C, W, and Y) were applied to the data observed in these 2 studies at 7 months of age, they would still be met for serogroups C, W, and Y in the US part of Study V59P14 (Study group US1) and in Study V59_33, and they would be met for all 4 serogroups in the LA subjects of Study V59P14 (Study group LA3).

In terms of non-interference data, from Study V59P14, non-inferiority of the immune responses elicited by routine infant vaccines Pediarix, ActHIB, and Prevnar administered concomitantly with MenACWY versus their administration alone was demonstrated in all key secondary analyses of all vaccine antigens tested except for the pneumococcal antigen PnC 6B (in US subjects, but not LA subjects [LL of the 95% CI around the vaccine group difference, -14%]) and the pertussis antigen PRN (in LA subjects, but not US subjects [LL of the 95% CI around the GMC ratio, 0.66]). In the key secondary analyses performed at 7 months of age for Pentacel, HBV vaccine and Prevnar in Study V59_33, the non-inferiority margins were met for all antigens assessed except for the pneumococcal antigens 6B and 23F and the pertussis antigens FIM and PT when assessed in terms of seroresponse. It should be noted that in Study V59_33, non-inferiority was demonstrated for all 4 pertussis antigens in the additional key secondary analysis based on GMC ratios.

As shown in Table 18, the data observed across Studies V59P21, V59P14, along with that from supportive Studies V59P9 and V59P7 strongly support the claim of efficacy of the proposed 2-dose catch-up schedule and allow for a considerable degree of flexibility in accommodating abbreviated catch-up vaccination schedules for older infants and toddlers who did not initiate the proposed, standard 4-dose schedule in early infancy. In all assessments made, the adequate immune response criteria pre-specified for the complete 4-dose MenACWY series in Studies V59P14 and V59_33 were achieved at 1 month after the 2-dose catch-up administration. The main dataset in support of the 2-dose catch-up schedule consisted of 492 infants composing the

PP populations of pivotal Studies V59P21 and V59P14 who had an available result for at least one serogroup. In Study V59P14, at 1 month after the 2 catch-up doses, 97% of the subjects achieved hSBA \geq 1:8 for serogroup A and 100% for serogroups C, W, and Y (Table 18).

Table 18: Studies V59P21, V59P14, V59P9, and V59P7, Data for the criteria met/failed the 95% CI around the Percentage of Subjects with hSBA \geq 1:8, 7

Study	MenACWY schedule ^b	Study Objective	Criteria ^a Met/Failed			
			Serogroup	Number of subjects	Point estimate (95% CI)	Criterion met/failed
V59P21	7-9, 12	co-primary	A	379	88% (84%, 91%)	√
			C	195	100% (98%, 100%)	√
			W	196	98% (96%, 100%)	√
			Y	198	96% (93%, 99%)	√
V59P9	6, 12	secondary (descriptive)	A	50	84% (71%, 93%)	√ ^c
			C	55	100% (94%, 100%)	√ ^c
			W	40	100% (91%, 100%)	√ ^c
			Y	53	100% (93%, 100%)	√ ^c
V59P14	12, 15	secondary (descriptive)	A	101	97% (92%, 99%)	√ ^c
			C	102	100% (96%, 100%)	√ ^c
			W	98	100% (96%, 100%)	√ ^c
			Y	95	100% (96%, 100%)	√ ^c
V59P7	12-24, 18-30	secondary (descriptive)	A	29	86% (68%, 96%)	√ ^c
			C	29	100% (88%, 100%)	√ ^c
			W	29	100% (88%, 100%)	√ ^c
			Y	29	100% (88%, 100%)	√ ^c

a: LL of the 95% CI around the percentage of subjects achieving hSBA \geq 1:8 at 1 month after the 2-dose series > 65% for serogroup A and > 85% for serogroups C, W, and Y (statistical criteria pre-specified for the V59P21 analysis only); b vaccination schedule expressed in terms of months of age; c results observed if the statistical criteria pre-specified for study V59P21 were applied to studies V59P14, V59P9, and V59P7, which had no pre-specified statistical criterion for assessing the 2-dose catch-up schedule (only descriptive statistics);

Data in support of the 2-dose MenACWY catch-up series proposed for older infants mainly come from Study V59P21, which was specifically designed (co-primary immunogenicity objective) to assess adequacy of the immune response elicited by 2 doses of MenACWY administered at 7 to 9 and at 12 months of age. Further data in support of a 2-dose series in older infancy come from Study V59P9. One month after completing the 2-dose catch-up series, with MenACWY administered at 6 and 12 months of age, 84% of the subjects achieved hSBA \geq 1:8 for serogroup A and 100% for serogroups C, W, and Y (Table 18). Further data in support of a 2-dose series in toddlers come from Study V59P7 (subjects receiving the first dose of MenACWY at 12- 24 months of age and 2nd dose 6 months later). One month after completing the 2-dose catch-up series, 86% of the subjects achieved hSBA \geq 1:8 for serogroup A and 100% for serogroups C, W, and Y (Table 18).

7.5. Evaluator's conclusions on clinical 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 CBER. Collectively, from these studies, the data also

support the claim that the first 3 doses of MenACWY can be administered concomitantly with DTaP, Hib, HBV, IPV, and CRM- containing pneumococcal vaccines (Prevnar and Prevnar 13) at 2, 4, and 6 months of age without risk of interference. Similar, data from the two dose studies and Study V59P20 supports the immunogenicity of the single dose course in children 2-10 years of age.

8. Clinical safety

8.1. Studies providing evaluable 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 (documented on 15 May 2009), CBER re-iterated their EOP2 guidance on the requirement to provide adequate infant safety data for licensure:

- a. that '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. that safety be assessed for 6 months following the final dose in the series;
- c. that 50% or more of the safety database be from US infants;
- d. that additional extended safety data (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.

8.1.1. Pivotal studies that assessed safety as the sole primary outcome

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

8.1.2. Pivotal and/or main efficacy studies

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

8.1.3. Other studies

8.1.3.1. Other efficacy studies

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

8.1.3.2. Studies with evaluable safety data: dose finding and pharmacology

Study V59P8

This was a Phase II, randomised, single-blind, controlled, single-centre study consisting of 2 parts. Part 1 was designed to compare safety and immunogenicity of a single dose of MenACWY to that of a licensed quadrivalent meningococcal polysaccharide vaccine (Menomune™) in children 2 to 10 years of age. Part 2, an open-label component of the study, evaluated the concomitant use of a single dose of MenACWY with routine toddler vaccines (Prevnar and commercially available DTaP vaccine) in subjects 12 to 23 months of age. The study was conducted from April 2005 to November 2006 in the US. The overall study population was stratified by age, as follows:

- i. children 2 to 10 years of age; and
- ii. toddlers 12 to 23 months of age, further stratified into subjects 12 to 15 and subjects 16 to 23 months of age.

The 12 to 15 months of age stratum received MenACWY with or without concomitant Prevnar, while the 16 to 23 months of age stratum received MenACWY with or without a commercially available DTaP vaccine. Overall, Study V59P8 enrolled a total of 910 subjects. Since Study V59P8 only explored immunogenicity after a single MenACWY dose, no immunogenicity data from this study are included in this submission; safety data collected following a single dose of MenACWY in the toddler population of Study V59P8 were included in the pooled safety analyses.

8.1.4. Studies that assessed safety as the sole primary outcome

8.1.4.1. Study V59P23

Study design, objectives, locations and dates

This Phase III study was an open-label, randomised, controlled safety trial in healthy children two months of age and older. Study vaccine was administered at 2, 4, 6, and 12 months of age. Subjects were randomised in a 3:1 ratio to receive either MenACWY + routine infant vaccines (RIV) concomitantly, or RIV alone. There were four study groups which included two pairs of treatment and control groups as shown in Tables 19 and 20. Subjects in Groups 1 and 2 were enrolled at sites located in the US, Asia and South America, while subjects in Groups 3 and 4 were enrolled at US sites only. The protocol specified safety monitoring/evaluation methods were different for Groups 1 and 2 (Non-detailed Safety Groups) compared to what was pre-specified for Groups 3 and 4 (Detailed Safety Groups). The study was conducted from December 2008 to November 2011 at 130 study sites in the US, 4 study sites in Taiwan, and 19 study sites in Latin America (Guatemala, Panama, Costa Rica, and Peru).

Table 19: Objectives and Design of Study V59P23

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

Table 20: Study VP59P23 visit design

Study Group	Visit 1 (2 mo.)	Visit 2 (4 mo.)	Visit 3 (6 mo.)	Phone Call 1 (9 mo.)	Visit 4 (12 mo.)	Visit 5 (15 mo.)	Phone Call 2 (18 mo.)
1 (ND)	Men ACWY + RIV	Men ACWY + RIV	Men ACWY + RIV	Safety Follow-up	Men ACWY + RIV	RIV	Safety Follow-up
2 (ND)	RIV	RIV	RIV	Safety Follow-up	RIV	RIV	Safety Follow-up
3 (D)	Men ACWY + RIV	Men ACWY + RIV	Men ACWY + RIV	Safety Follow-up	Men ACWY + RIV	RIV	Safety Follow-up
4 (D)	RIV	RIV	RIV	Safety Follow-up	RIV	RIV	Safety Follow-up

Primary Objective

1. To compare the percentage of subjects, during days 1-7 after any vaccination, with at least one severe systemic reaction after administration of MenACWY plus routine vaccine [study group 3] with the percentage of subjects presenting with at least one severe systemic reaction after routine vaccines alone [study group 4] at 2-,4-,6- and 12 months of age.

Secondary Objectives:

1. To compare the percentage of subjects with at least one serious adverse event (SAE) through 6 months post-final dose in subjects who receive MenACWY with routine vaccinations [Study Groups 1 and 3] to the percentage in those subjects receiving routine vaccinations alone [Study Groups 2 and 4].
2. To assess the safety and tolerability of MenACWY through 6 months post-Final dose when given concomitantly with routine infant vaccines.

Inclusion and exclusion criteria

The study population consisted of healthy 2-month-old infants (aged 55-89 days) born after a full-term pregnancy with an estimated gestational age ≥ 37 weeks and a birth weight ≥ 2.5 kg; whose parent/legal representative gave written informed consent after the nature of the study had been explained. Other inclusions and exclusions as in 7.2.1.2.

*Study treatments**Investigational vaccine*

MenACWY (MenACWY): Each 0.5 mL dose contains 10 μ g MenA oligosaccharide, 5 μ g of each of MenC, MenY and MenW-135 oligosaccharides and a total of 32.7 to 64.1 μ g of CRM197 protein. The vaccine contains no preservative or adjuvant. To be given intramuscularly (IM).

Concomitant vaccines

Subjects enrolled received concomitant routine infant vaccinations as recommended by the Advisory Committee on Immunization Practices (ACIP) in the USA or equivalent in other countries. This included DTaP-IPV-Hib vaccine (Pentacel; Aventis Pasteur, Inc), 7-valent pneumococcal conjugate vaccine (Prevnar 7; Pfizer, Inc), MMR vaccine (MMR-II; Merck & Co, Inc), Rotavirus (Rotateq, Merck & Co., Inc), Hepatitis B (Recombivax HB), Varicella (Varivax, Merck & Co., Inc), and a Hepatitis A virus vaccine. Pentacel was the only required vaccine, and may have been supplied to sites by the sponsor for the first 3 doses for subjects enrolled in Groups 3 or 4.

Subjects enrolled in other countries were required to receive DTaP-IPV-Hib, PCV7 and MMR vaccines, and if required, country specific vaccinations. The applicant supplied commercial batches of varicella vaccine (Costa Rica only) and DTaP-HBV-IPV/Hib (Infanrix Hexa; GSK Biologicals) and DTaP-IPV/Hib (Infanrix Penta; GSK Biologicals), PCV7, MMR (Priorix; GSK

Biologicals) to Costa Rica, Guatemala, Peru and Panama. Sites in Taiwan administered DTaP-IPV/Hib (Infanrix Penta) or DTaP-IPV/Hib (Pediace), PCV7 and MMR (Priorix).

In order to provide additional details regarding the safety data collection process and address concerns about rates of adverse events (AEs) observed in the V59P23 study, submitted in interim analysis, Novartis undertook an extensive and robust data collection project that included the majority (126 of 130) of the US V59P23 study sites. This project is referred to as the 'Menveo Metadata Collection' (MMC) project, sought to collect additional pre-existing data from each study site regarding how and when safety events were collected through a comprehensive review of all available source documentation. As an outcome of the MMC project, Novartis performed additional analyses of the safety data. New populations were defined for analysis of solicited and unsolicited events:

- **US As Treated Safety Population:** This population includes exposed subjects who participated in MMC (126 of 130 US sites). For the assessment of solicited events this population had to have documented reactogenicity data for a respective study period. Subjects enrolled at Site 023 were excluded from this population when solicited events were assessed.
- **Restricted Safety Set (RSS):** For evaluation of solicited events, this population is a subset of US As Treated Safety Population, found to have diary cards that were returned to the site as specified in the protocol with no evidence of solicited AE recall. Subjects from Site 023 were also excluded from this population. For evaluation of unsolicited events this population is a subset of US As Treated Safety population from which the unsolicited AEs were recorded on a diary card/worksheet that had been returned to the site.

The primary goal of the MMC project was to collect additional details on the safety data collected during the 3 pivotal studies included in the MenACWY infant submission to allow for additional analyses to evaluate how diary card reporting affects the rates of solicited events. Because of this, it was possible to restrict the MMC project for V59P23 to subjects enrolled at US sites. Restriction of the MMC project for V59P23 to US enrolled subjects also allowed for completion of the planned analyses for unsolicited events, as approximately 50% of the subjects in V59P23 were enrolled at US sites.

Safety variables and outcomes

All subjects

Participants were monitored for immediate adverse reactions that occurred during the 15-minute observation period after each vaccination.

Subjects who had withdrawn from the study prematurely were contacted 6 months after the last study vaccine dose for safety follow-up if consent had not been withdrawn. All SAEs were followed to resolution or as deemed appropriate by the investigator or medical monitor.

Study groups 1 and 2

SAEs and MAAEs (unsolicited AE that results in a visit to a medical office or emergency room visit) were assessed from the time of informed consent through study end (18 months of age).

Study groups 3 and 4

Pre-specified local and systemic adverse reactions assessed within the first 7 days after each vaccination, along with defined grading (mild-severe). These were as follows (and apply to all studies included in the pooled data):

Solicited Local (Injection site) Adverse Reactions

- Tenderness
- Erythema

- Induration

Systemic Adverse Reactions

- Change in Eating Habits
- Sleepiness
- Persistent Crying
- Vomiting
- Diarrhoea
- Irritability
- Rash
- Axillary Temperature

Randomisation and blinding methods

This was an open study. Randomisation as in Section 7.2.1.5.

Analysis populations

Analysis of the primary objective was based on the As Treated Safety Population.

Sample size

Assuming that the true rate of severe systemic reactions in each group is 6% and an estimated 10% drop-out rate, a sample size of 1250 subjects in the MenACWY + RIV group and 417 in the RIV group would enable a study power of >99%. If the true rate was 14% in each group, then the study power would be 91%.

Statistical methods

The primary objective of the study, non-inferiority of the rate of severe systemic reactions in subjects vaccinated concomitantly with MenACWY and routine vaccines compared to subjects immunized with routine vaccines alone would be proven if the upper limit of the two-sided 95% CI of the difference (MenACWY vaccine and routine vaccines group minus routine vaccines alone group) in the proportion of subjects experiencing at least one severe systemic reaction during the first 7 days (Days 1-7) after any vaccination was <6%. The study would be considered a success if the rate of severe systemic reactions for MenACWY given concomitantly with routine vaccines was shown to be non-inferior to routine vaccines only.

Participant flow

The study enrolled a total of 7744 subjects 2 months of age, who were randomised at a 3:1 ratio to receive either MenACWY concomitantly with routine infant/toddler vaccines (5772 enrolled subjects) or routine vaccines alone (1972 enrolled subjects). Of the 3854 subjects that were enrolled at US sites and approximately 2855 subjects were enrolled in Groups 1 and 3 (MenACWY administered concomitantly with RIV) and 999 subjects were enrolled in Groups 2 and 4 (RIV only). Included in the applicant's detailed safety population were 1409 subjects in the MenACWY+ RIV arm (Group 3) and 489 in the control arm (Group 4).

Of the 7744 subjects enrolled in the study, 6692 subjects completed the protocol and 1052 subjects terminated early from the study. The most frequent reasons for early termination were lost to follow-up, withdrawal of consent, and administrative reasons. Of the 7744 subjects enrolled in the study, 6692 subjects completed the protocol and 1052 subjects terminated early from the study. The most frequent reasons for early termination were lost to follow-up, withdrawal of consent, and administrative reasons.

Major protocol violations/deviations

In the MenACWY + RIV groups, 48% of subjects (2755/5771) had a protocol deviation compared to 49% (966/1973) of subjects in the control groups. In both groups, there were <1% major protocol deviations however the only protocol violation categorised as major was 'no exposure to any vaccine.' These subjects (n=16) were excluded from the safety population.

The most common protocol deviation was 'received protocol-specified vaccines out of window' which was seen in 31-32% of all subjects across groups. The majority of the subjects received the protocol-specified vaccines within a few days (for example, within 3 days) of the pre-specified immunisation window. This was followed by early termination and minor procedural deviation during safety follow-up, which were seen in 14% and 12% of all subjects across groups, respectively. Reasons for minor procedural deviation were mainly due to subject did not have a 9 month or 18 month safety follow-up phone call done, or had these phone calls done out of window. The majority of these deviations were classified as a minor deviation, and thus not excluded from the safety analysis.

Baseline data

The demographic and baseline characteristics of subjects included in the US As Treated Safety Population are presented in Table 21. Demography of the US As Treated Safety Population did not differ with the As Treated Safety Population (inclusive of all subjects).

Table 21: Summary of Demography – US As Treated Safety Population

	ACWY-ND N=1431	RVAX-ND N=507	ACWY-D N=1394	RVAX-D N=484	ACWY-All N=2825	RVAX-All N=991
Age (Days):	65.2±7.0	65.2±6.6	65.4±6.5	65.2±6.3	65.3±6.8	65.2±6.5
Sex:						
Male	749 (52%)	266 (52%)	684 (49%)	255 (53%)	1433 (51%)	521 (53%)
Female	682 (48%)	241 (48%)	710 (51%)	229 (47%)	1392 (49%)	470 (47%)
Race:						
Asian	24 (2%)	7 (1%)	31 (2%)	9 (2%)	55 (2%)	16 (2%)
Black	181 (13%)	71 (14%)	165 (12%)	49 (10%)	346 (12%)	120 (12%)
Caucasian	904 (63%)	313 (62%)	893 (64%)	317 (65%)	1797 (64%)	630 (64%)
Hispanic	197 (14%)	69 (14%)	208 (15%)	80 (17%)	405 (14%)	149 (15%)
Other	125 (9%)	47 (9%)	97 (7%)	29 (6%)	222 (8%)	76 (8%)
Weight (kg):	5.44±0.66	5.43±0.68	5.42±0.68	5.41±0.65	5.43±0.67	5.42±0.66
Height (cm):	58.60±2.46 (N=1430)	58.62±2.48 (N=506)	58.55±2.52 (N=1393)	58.45±2.46	58.58±2.49 (N=2823)	58.54±2.47 (N=990)

8.1.4.2. Results for the primary safety outcome

In the cohorts of subjects who returned the diary cards to the sites, the results of primary safety analysis showed that 15% of subjects in the ACWY-D group and 12% of subjects in the RVAX-D group having at least one severe systemic reaction (Table 22). The vaccine group difference was 3.0% with the upper limit of the two-sided 95% confidence interval around the difference of 6.3%. In the restricted safety population who returned diary cards per protocol without evidence of recall (designated as Restricted Safety Set for solicited AEs assessment), the percentages of subjects experiencing any severe systemic solicited event were 12% and 10%, respectively (Table 23), with a vaccine group difference of 1.7% and the upper limit of the two-sided 95% confidence interval around the difference of 4.9%. The non-inferiority criterion defined in the V59P23 protocol was met in the population of subjects who returned diary cards per protocol with no signs of recall, but was not met in the population who returned diary cards regardless of status of solicited data recall.

Table 22: 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

Table 23: 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

Results for other safety outcomes

The relative risk (ACWY-D: RVAX-D) of at least one severe systemic reaction was 1.24 with a two-sided 95% confidence interval of [0.94, 1.62]. The risk of at least one severe systemic reaction during days 1 through 7 after any vaccination was at most 62% higher in the ACWY-D group (was less than two-fold higher) than in the RVAX-D group.

Rates of systemic reactions of any severity during days 1 through 7 after any vaccination were similar between the vaccine groups. Rates of any severe systemic reaction during days 1 through 7 after each vaccination were low. The upper limit of the two-sided 95% confidence interval for the risk difference was $\leq 4.3\%$ for severe systemic reactions during days 1 through 7 after each of the four individual vaccinations, below the 6% non-inferiority criterion for the upper two-sided 95% CI for the overall ACWY-D minus RVAX-D rate difference.

The most common systemic reactions were irritability (76% - 78%) followed by sleepiness (66% - 69%) with $\leq 6\%$ of the subjects reporting severe reactions. Within the systemic reactions, the largest difference between the two vaccination groups was in rates of diarrhoea and vomiting.

MenACWY was less locally reactogenic than the pneumococcal conjugate vaccine. Most of the local and systemic reactions were mild to moderate in severity for both vaccination groups.

The percentages of subjects with solicited local and systemic reactions declined after each subsequent vaccination and were lowest after the third infant vaccination.

Overall, 90% - 92% of subjects reported at least one AE. The most commonly reported AEs by preferred term were upper respiratory tract infections (54% - 55%, similar for each vaccination group). Few (4% - 5%) subjects reported serious AEs and the majority of them were not related to the study vaccine. Very few (<1% 1%) subjects reported AEs that led to the premature withdrawal from the study.

Two unexpected possibly related SAEs (Inguinal abscess and Epilepsy) were reported during the study. An additional two events (both Kawasaki's Disease) are discussed in a later section. There were five deaths reported in the study, all in subjects randomised to MenACWY. A diverse range of aetiologies and time latency from vaccination were reported. None were assessed as related to the vaccine.

8.1.4.3. Evaluator commentary

The percentages of subjects experiencing at least one severe systemic reaction were similar between the ACWY-D (MenACWY plus routine vaccines) and RVAX-D (routine vaccines only) groups. Overall reported rates were 15.3% in the ACWY-D group and 12.4% in the RVAX-D group. Significant centre and vaccination group by centre differences were found in this study.

The reason for the significant centre differences and vaccination group by centre is unexplained, but may have been due to reporting bias.

The MenACWY vaccine was less locally reactogenic than the comparator pneumococcal conjugate vaccine. The profile of systemic reactions to MenACWY vaccine given along with routine vaccines was similar to the profile of systemic reactions for routine vaccines given alone, except for a higher percentage of subjects developing diarrhoea and vomiting in the MenACWY vaccine plus routine vaccines group. The majority of the local and systemic reactions were mild to moderate in severity and the percentage of subjects reporting local and systemic reactions decreased with subsequent vaccinations in each of the vaccination groups. Overall, the percentages of subjects reporting any unsolicited AEs or SAEs were similar in each vaccination group. SAEs that were related (possibly or probably related) to MenACWY and AEs leading to premature withdrawal were rare; none of the five deaths that occurred during the trial were suspected to be related to the study vaccination.

8.2. 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 24), of whom 3466 provided detailed safety data through one month post- dose 4. All subjects were to be followed for 6 months post- dose 4. Across the 3 studies, US subjects contributed 55% of the detailed safety data, and 44% of all safety data through dose 4.

The 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) Good Clinical Practice (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 (Table 25). 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) as shown in Tables 26-29.

Table 24: 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 25: 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.

Table 26: Safety in children, 2-10, Studies and Monitoring Periods

Study	Solicited AEs, other indicators of reactogenicity, and all unsolicited AEs	Medically significant AEs ^a	AEs necessitating a physician's visit	SAEs and AEs leading to premature withdrawal
V59P7 (2 vacc)	Days 1 to 7 after each vaccination	–	throughout the study	throughout the study
V59P8 (1 vacc)	Days 1 to 7	throughout the study	Days 1 to 29	throughout the study
V59P10 ^b (1 vacc)	Days 1 to 7	throughout the study	Days 1 to 29	throughout the study
V59P20 (1/2vacc)	Days 1 to 7 after each vaccination	throughout the study	Days 1 to 29 after each vaccination	throughout the study

1 vacc = single vaccination schedule; 2 vacc = 2-vaccination schedule; 1/2=study with single-and 2-vaccination schedule arms; SAE=serious adverse event. a AEs requiring a physician's visit, Emergency Department visit, or leading to withdrawal, excluding preplanned visits, medical office visits, or Emergency Room visits for routine medical care and common acute conditions (e.g. upper respiratory tract infection, otitis media, pharyngitis, urinary tract infection, gastroenteritis, superficial skin infection, contact dermatitis); b in study V59P10, common childhood exanthematous diseases were also collected on days 1 to 29.

Table 27: Overview of Reactogenicity: % of Children Reporting Solicited AEs (Local and Systemic Reactions), by Age, by Vaccination, Pooled Analysis

Reaction	1 st Vaccination									
	2-5 years ^a				6-10 years ^b			2-10 years ^c		
	MenACWY N=1870	Menactra N=684	Menomune N=418	Mencevax N=74	MenACWY 1237	Menactra N=571	Menomune N=443	MenACWY N=3107	Menactra N=1255	Menomune N=861
Any Reaction	57%	62%	49%	57%	54%	60%	49%	56%	61%	49%
Any Local Reaction	43%	46%	33%	51%	45%	53%	40%	43%	49%	36%
Any Systemic Reaction	35%	39%	29%	26%	27%	28%	22%	32%	34%	25%
	2 nd Vaccination (2-5 years)									
	MenACWY→MenACWY ^d N=550					Mencevax→MenACWY ^e N=74				
Any Reaction	49%					43%				
Any Local Reaction	37%					35%				
Any Systemic Reaction	27%					14%				

a: vMenACWY: studies V59P7, V59P8, V59P10, and V59P20, Menactra: study V59P20; Menomune: studies V59P8 and V59P10; Mencevax: study V59P7 (only 3-5 years age group); b: MenACWY: studies V59P8, V59P10, and V59P20; Menactra: study V59P20; Menomune: studies V59P8 and V59P10; c: MenACWY: studies V59P7 (only 2-5 years age group, the comparator, Mencevax, administered only in the 3-5 years age group, is presented in the 2-5 years fields of this table), V59P8, V59P10, and V59P20; Menactra: V59P20, Menomune: studies V59P8 and V59P10; d: Studies V59P7 and V59P20; e: Study V59P7.

Table 28: Percentages of Children Ages 2-10 Reporting Any and (Severe) Local Reactions after First/Single Meningococcal Vaccination, Days 1-7 and 1-3, Pooled Analysis

Reaction	MenACWY		Menactra		Menomune	
	1-7 N=3107	1-3 N=3107	1-7 N=1255	1-3 N=1255	1-7 N=861	1-3 N=861
Pain ^a	31% (15,<1%)	30% (15,<1%)	40% (1%)	39% (1%)	28% (1,<1%)	27% (1,<1%)
Erythema (>50mm)	23% (4%)	23% (4%)	24% (3%)	23% (3%)	11% (0)	10% (0)
Induration (>50mm)	16% (2%)	16% (2%)	16% (2%)	16% (2%)	8% (0)	8% (0)

Table 29: Percentages of Children Ages 2 to 10 Reporting Any and (Severe) Systemic Reactions after First/Single Meningococcal Vaccination, Days 1 to 7 and 1 to 3, Pooled Analysis

Reaction	MenACWY		Menactra		Menomune	
	1-7 N=3107	1-3 N=3107	1-7 N=1255	1-3 N=1255	1-7 N=861	1-3 N=861
Chills	5%(1,<1%)N=1236	4%(0)N=1235	5%(2,<1%)N=571	3%(1,<1%)N=571	5%(1,<1%)N=443	4%(0)N=443
Nausea	6%(5,<1%)N=1236	4%(3,<1)N=1235	6%(2,<1%)N=571	5%(2,<1%)N=571	4%(2,<1%)N=443	3%(1,<1%)N=443
Malaise	12%(1%)N=1236	9%(1%)N=1235	11%(1%)N=571	8%(1%)N=571	8%(1,<1%)N=443	7%(0)N=443
Myalgia	9%(1%)N=1236	8%(5,<1%)N=1235	10%(1%)N=571	9%(1%)N=571	7%(1,<1%)N=443	6%(0)N=443
Arthralgia*	4%(6,<1%)N=2882	4%(3,<1%)N=2882	4%(2,<1%)	4%(1,<1%)	4%(1,<1%)	3%(1,<1%)
Headache*	11%(11,<1%)N=2882	8%(7,<1%)N=2882	9%(1%)	8%(6,<1%)	10%(2,<1%)	7%(0)
Rash*	5%(2% ^b)N=1626	4%(2% ^b)N=1626	4%(2% ^b)	3%(1% ^b)	--	--
Change in eating habits	10%(7,<1%) N=1842	7%(4,<1%) N=1840	10%(2,<1%) N=671	8%(1,<1%) N=667	10%(0) N=415	7%(0) N=415
Sleepiness	14%(1%)N=1869	12%(7,<1%)N=1869	18%(1%)N=684	17%(2,<1%)N=683	9%(1,<1%)N=418	7%(1,<1%)N=418
Irritability	18%(1%)N=1868	16%(1%)N=1868	22%(1%)N=684	20%(1%)N=683	11%(0)N=418	9%(0)N=418
Vomiting	4%(3,<1%)N=1869	2%(2,<1%)N=1869	3%(0)N=684	2%(0)N=683	4%(0)N=418	2%(0)N=418
Diarrhea	7%(3,<1%)N=1869	5%(1,<1%)N=1869	8%(0)N=684	6%(0)N=683	6%(0)N=418	4%(0)N=418
Fever ^c	4%(1%)N=3106	2%(7,<1%)N=3106	2%(4,<1%)N=1254	1%(2,<1%)N=1254	5%(1%)	2%(1%)

8.3. Adverse events

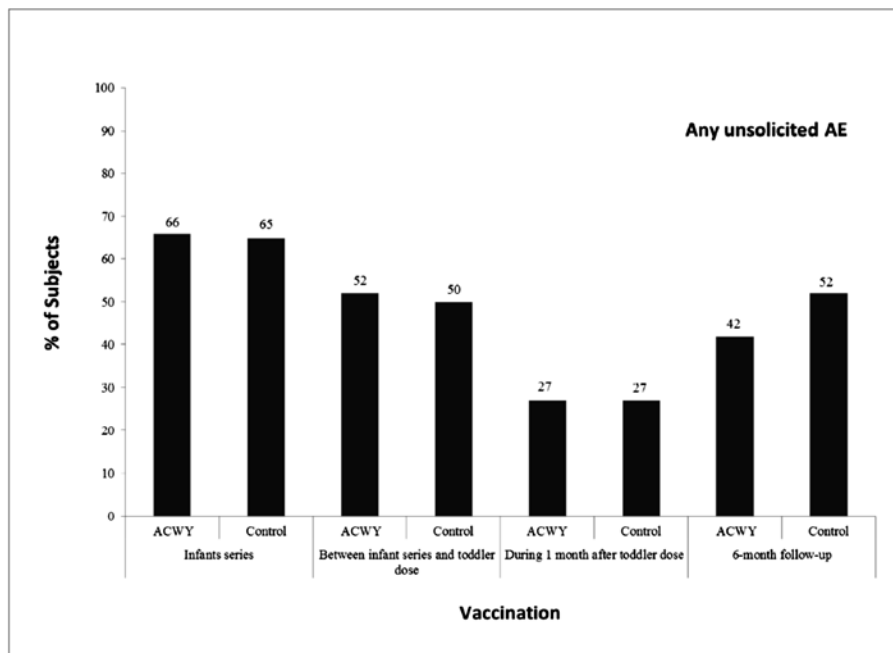
8.3.1. All adverse events (irrespective of relationship to study treatment)

8.3.1.1. Integrated safety analyses

Infants and Toddlers

No noteworthy differences in the percentages reporting any unsolicited AEs (V59P14, V59P23, and V59_33) were observed between the MenACWY and control groups when analysed during the infant series vaccinations (66% versus 65% for MenACWY and control, respectively), between infant series and toddler dose (52% versus 50%), and for 28 days following the toddler dose (27% versus 27%, all respectively; Figure 1). During the 6-month follow-up period a lower percentage of subjects in the MenACWY group (42%) than the control group (52%) experienced unsolicited AEs. The percentages of catch-up subjects who experienced any unsolicited AEs (V59P8, V59P9, V59P14, and V59P21) were generally lower than those for the younger infant subjects.

Figure 1: Overview of Unsolicited AEs by Time Period, Safety Population, All Infants (V59P14, V59P23, and V59_33)



Infant series: N = 8735 and 3749 for MenACWY and control, respectively; Between infant series and toddler dose: N = 8168 and 3468; During 1 month after toddler dose: N = 7812 and 2600; 6-month follow-up: N = 7716 and 2296.

Children (2-10)

The safety profile of MenACWY was evaluated in four studies conducted in children aged 2-10 years. In the overall 2 to 10 years age group, the percentage of subjects reporting unsolicited AEs (any and possibly related) within 1 month of the first/single meningococcal vaccination were similar after MenACWY and comparator vaccines Menactra and Menomune (any: range, 18% to 21%, possibly related: range, 3% to 5%). When one dose of meningococcal vaccine was administered in the 2 to 5 years age group, similar percentages of subjects reported unsolicited AEs (any and possibly related) within 1 month of receiving MenACWY, Menactra, or Menomune (any: range, 20% to 24%, possibly related: range, 3% to 5%). The percentage of Mencevax recipients reporting AEs regardless of relatedness (31%) was higher than the percentages observed for MenACWY, Menactra, and Menomune; conversely, no Mencevax recipient reported possibly related AEs within 1 month of vaccination.

When two doses of meningococcal vaccine were administered in the 2 to 5 years age group, the percentages of subjects reporting unsolicited AE (any and possibly related) within 1 month of the second vaccination were similar regardless of whether the first vaccine administered was MenACWY or Mencevax (any: 19% in both vaccine groups, possibly related: 2% and 1% after two doses of MenACWY and after Mencevax, MenACWY, respectively).

The results observed in the 6 to 10 years age group showed a trend similar to that seen in the overall 2 to 10 years population. Overall, the reporting rates observed in the 6 to 10 years age group for unsolicited AEs irrespective of relatedness were lower than those observed in the younger, 2 to 5 years age group, while the rates observed for possibly or probably vaccine-related unsolicited AEs were similar in the two age strata. The safety results for both age groups and combined, local and systemic reactions are shown in Tables 27-29. Overall, the analysis of unsolicited AEs did not raise any clinical concerns regarding any time period after administration of MenACWY. The majority of unsolicited AEs were assessed by the investigators as unrelated to the study vaccines. The majority of unsolicited AEs assessed as at least possibly vaccine-related were mild to moderate in severity and were mostly caused by:

- local/systemic AEs persisting past the 7-day observational period;
- common side effects of vaccination observed in children; or
- common illnesses typical of the paediatric population.

8.3.2. Treatment related adverse events (adverse drug reactions)

8.3.2.1. Integrated safety analyses

Solicited and unsolicited AEs were assessed in all studies with the following definitions:

- Solicited AEs were those that were assessed systematically through the use of diary cards during the 7 days following a vaccination.
- Unsolicited AEs were those that were reported spontaneously or in response to general health questions, and included any AEs, medically attended AEs, medically significant AEs, and Serious AEs (SAEs).

Infants/Toddlers

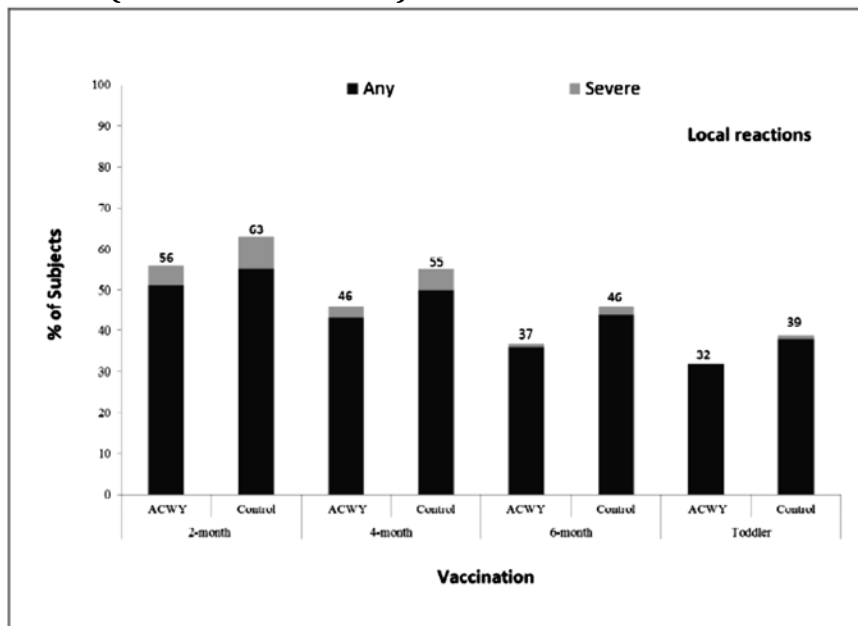
Overall, for all 4-dose infant subjects (V59P14 and V59P23), the percentages of subjects who experienced any solicited AEs and any systemic AEs were similar between the MenACWY and control groups after each vaccination. In general, almost all subjects in the MenACWY (plus routine paediatric vaccinations) and control groups experienced some kind of solicited AE during their participation in the studies. The percentages of all 4-dose infant subjects who experienced any solicited AEs were the same between the MenACWY (96%) and control (96%) groups, while the percentage of subjects who experienced any severe solicited AEs was somewhat lower in the MenACWY group (19%) than control group (22%) (Table 30:). Local AEs were experienced by a lower percentage of subjects in the MenACWY group (74%) than control group (79%) and severe (or > 50 mm) local AEs were also experienced by a lower percentage of subjects in the MenACWY group (8%) than control group (12%). Systemic AEs were experienced by similar percentages of subjects in both groups (88% and 87%) as well as severe systemic AEs (14% in both groups).

Table 30: Pooled safety analysis, percentage of Subjects Reporting any (and Severe) Local and/or Systemic AEs, after any Vaccination – Infants (V59P14 and V59P23)

		Total 4D ACWY	Total 4D CTRL	4D ACWY (US)	4D CTRL (US)	4D ACWY (non-US)	4D CTRL (non-US)
		N = 3932	N = 1065	N = 2243	N = 714	N = 1689	N = 351
Any AE	Any	3759 (96%)	1020 (96%)	2129 (95%)	677 (95%)	1630 (97%)	343 (98%)
	Severe	732 (19%)	231 (22%)	388 (17%)	140 (20%)	344 (20%)	91 (26%)
Local	Any	2904 (74%)	840 (79%)	1502 (67%)	527 (74%)	1402 (83%)	313 (89%)
	Severe or > 50 mm	304 (8%)	124 (12%)	114 (5%)	66 (9%)	190 (11%)	58 (17%)
Systemic	Any	3449 (88%)	930 (87%)	1990 (89%)	622 (87%)	1459 (86%)	308 (88%)
	Severe	542 (14%)	145 (14%)	321 (14%)	96 (13%)	221 (13%)	49 (14%)
Analgesic use	Any	3227 (82%)	857 (80%)	1799 (80%)	568 (80%)	1428 (85%)	289 (82%)

Local and Systemic AEs were: tenderness, erythema, induration, change in eating, sleepiness, persistent crying, irritability, vomiting, diarrhoea, fever, rash. Severe induration/erythema: > 50 mm; severe fever: $\geq 39.0^{\circ}\text{C}$. Rash not included in severe systemic summary because severity is not assessed. Post injection reaction data collected starting from 6 hours to 7 days after vaccination. A subject is only counted once in each category in this table. V59P5 is not included in this table because severity was not collected.

The percentages of subjects who experienced any local AEs were consistently lower in the MenACWY group than the control group after each vaccination: 2 months (56% versus 63%), 4 months (46% versus 55%), 6 months (37% versus 46%), and in the toddler year (32% versus 39%; Figure 2). The percentages of subjects reporting any systemic AEs were similar between the MenACWY and control groups following the 2-month vaccination (75% and 74% for MenACWY and control, respectively), the 4-month vaccination (61% in both groups), the 6-month vaccination (50% and 51%, respectively), and the toddler dose (47% in both Groups).

Figure 2: Percentage of Subjects Reporting Any (and Severe) Local AEs, by Vaccination – Infants (V59P14 and V59P23)

N = 3882 and 1734 for MenACWY and control at 2-month; 3738 and 1656 at 4-month; 3493 and 1564 at 6-month; 3178 and 887 at toddler.

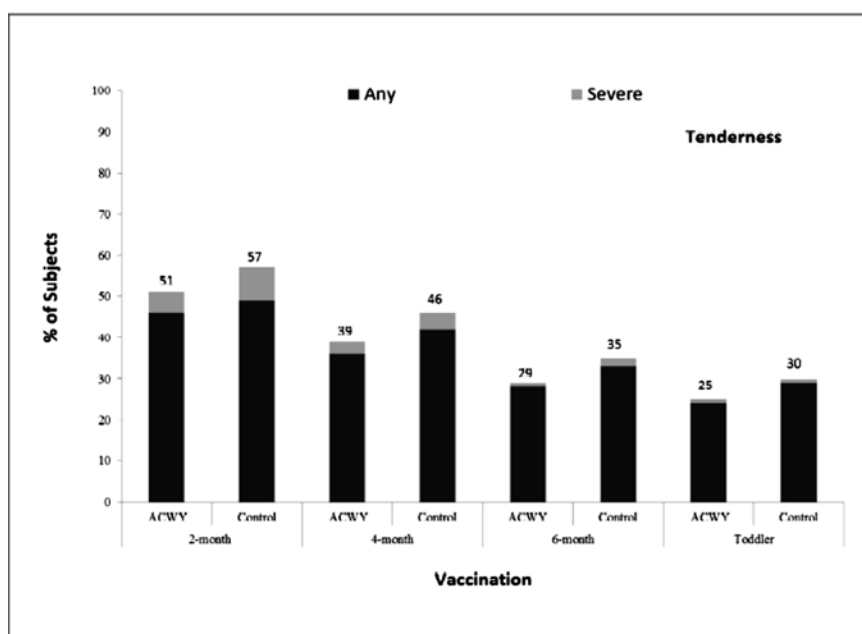
Local AEs after each vaccination (all infants)

Subjects in the MenACWY group experienced lower rates of tenderness, erythema, and induration than control subjects after each of the 4 vaccinations. The percentages of all 4-dose infant subjects who experienced tenderness day 1 (6 hours) to Day 7 following vaccinations were consistently lower in the MenACWY group than the control group following the 2-month

vaccination (51% versus 57% for MenACWY and control, respectively), the 4-month vaccination (39% versus 46%), the 6-month vaccination (29% versus 35%), and the toddler dose (25% versus 30%; Figure 3).

Within each group, the rates of any tenderness decreased with each subsequent vaccination. The percentages of subjects with severe tenderness following the first vaccination at 2 months appeared lower in the MenACWY group (5%) than the control group (8%), then were similar for subsequent vaccinations. The percentages of subjects who experienced erythema were consistently lower in the MenACWY group than the control group following each vaccination (range, 6% to 7% lower; Figure 3). The percentages of subjects who experienced severe erythema (> 50 mm) were low in both groups ($\leq 0.2\%$ in all cases except in the control group following the 2-month vaccination [0.7%]); Similarly, the percentages of subjects who experienced induration were consistently lower in the MenACWY group than the control group following each vaccination (range, 5% to 9%). The percentages of subjects who experienced severe induration (> 50 mm) were low in both groups ($\leq 0.2\%$ after each vaccination).

Figure 3: Percentages of Subjects Reporting Tenderness, Day 1 (6 hours) to Day 7 after Each Vaccination – Infants (V59P14 and V59P23)

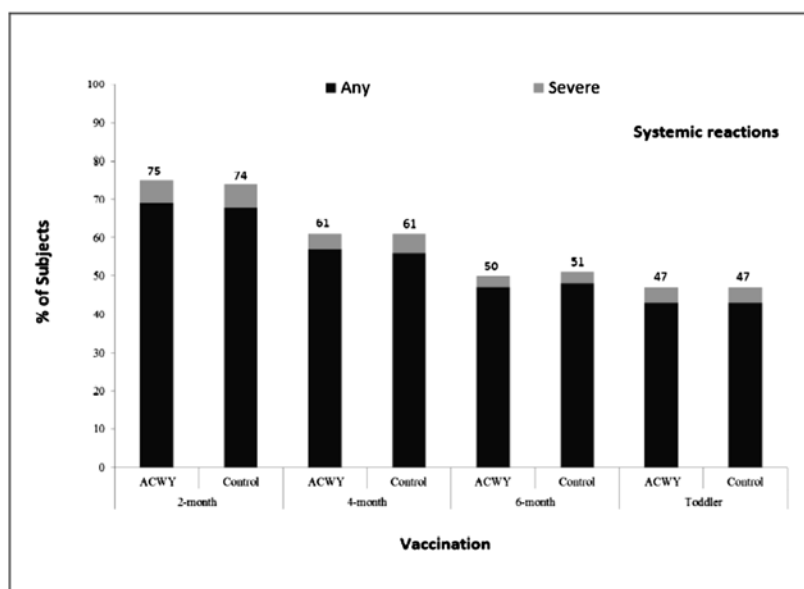


N = 3868 and 1723 for MenACWY and control at 2-month; 3723 and 1640 at 4-month; 3470 and 1557 at 6-month; 3161 and 879 at toddler.

Systemic AEs after each vaccination (all infants)

The percentages of subjects who experienced any systemic AEs day 1 (6 hours) to Day 7 after each vaccination were very similar between the MenACWY and control groups (Tables 29 and 30, Figure 4). Also, in general, these percentages appeared to decrease with each successive vaccination for all solicited AEs with the exception of fever and rash. Fever was experienced by similar percentages for both groups after each vaccination (range, 8% to 12%). Rash was low and consistently between 3% and 5% for both MenACWY and control groups at each vaccination. The most common systemic AEs were sleepiness (49% in both the MenACWY and control groups after the first vaccination, decreasing to 22% in both groups after the fourth vaccination), irritability (48% in both the MenACWY and control groups, decreasing to 29% and 32% after the fourth vaccination), and persistent crying (37% and 36%, decreasing to 14% and 15%); The percentages of severe AEs were low, never exceeding 3% for any solicited reaction in either group. Fever $\geq 40^{\circ}\text{C}$ occurred in < 1% of subjects in both groups across vaccinations.

Figure 4: Percentage of Subjects Reporting Any (and Severe) Systemic AEs, by Vaccination – Infants (V59P14 and V59P23)



N = 3882 and 1734 for MenACWY and control at 2-month; 3738 and 1656 at 4-month; 3493 and 1564 at 6-month; 3178 and 887 at toddler.

Catch up subjects

For the catch-up subjects, the percentages of subjects who experienced any local or systemic AEs were higher following the first dose (65%) than after the second dose (53%). This was also true for local AEs (31% and 25% following dose 1 and dose 2, respectively), systemic AEs (50% and 39%), and analgesic use (33% and 24%, all respectively). Local AEs after each vaccination (catch-ups): The percentages of subjects who experienced any tenderness, erythema, or induration were 2 to 3% higher following a first dose than after a second dose. The percentages of subjects who experienced severe tenderness or erythema/induration > 50 mm after each vaccination were low in all cases ($\leq 1\%$).

Systemic and local AEs after each vaccination (catch-ups)

The most common systemic AEs reported were irritability (33% and 24% after one dose and 2 doses, respectively) and sleepiness (23% and 16%, respectively). In general it appeared that the reported rates of systemic AEs were lower for the second dose than for the first dose in the catch-up series. There were differences between the regions. The percentages of subjects who experienced any local reactions were lower in the US subset than the non-US subset after vaccinations at 2 months, 4 months, and 6 months, but not following the toddler dose, for both MenACWY and Control recipients. Conversely, percentages of subjects who experienced any systemic reactions were higher in the US subset than the non-US subset following vaccinations at 4 months, 6 months, and the toddler dose, while they were similar following vaccination at 2 months.

Children (2-10 years)

In the overall 2 to 10 years age group, the percentage of subjects reporting any sign of reactogenicity was lowest after Menomune (49%). This tendency was observed both for local and systemic reactions (Table 27). The percentages of subjects reporting any sign of reactogenicity were slightly lower after MenACWY than after Menactra (56% versus 61%). This tendency was observed for local reactions, while similar percentages of MenACWY and Menactra recipients reported systemic reactions. After the first dose of meningococcal vaccine administered in the 2 to 5 years age group, similar percentages of subjects reported any sign of

reactogenicity after MenACWY, Menactra, and Mencevax (range, 57% to 62%) while the percentage observed for Menomune was lower (49%). There were no major differences in the percentages reporting local or systemic reactions after MenACWY versus Menactra, while the percentages were consistently lower after Menomune.

When two doses of meningococcal vaccine were administered in the 2 to 5 years age group, somewhat higher percentages reported any sign of reactogenicity after two doses of MenACWY than after Mencevax then MenACWY (49% versus 43%, Table 27). This was largely accounted for by a higher percentage of subjects reporting systemic reactions after two doses of MenACWY than after Mencevax followed by MenACWY (27% versus 14%), while the reporting rates for local reactions were similar in the two vaccine groups.

Local reactions in children

During the 7-day reporting period following the first/single meningococcal vaccination, in the overall 2 to 10 years age population, pain was the most commonly reported local reaction. Pain of any severity was reported by similar percentages after MenACWY and Menomune (31% and 28%, respectively), while the reporting rates observed for Menactra were higher (40%). Reports of severe pain were similar and low in all vaccine groups (range, <1% to 1%). Erythema and induration (any and severe [that is, >50mm]) were reported by similar percentages after MenACWY and Menactra and by considerably lower percentages after Menomune (Table 28).

Across the vaccine groups, in the majority of subjects, local solicited reactions (any and severe) occurred within the first 3 days post vaccination: no more than a 1% difference in the percentages reporting local reactions of any severity was observed for days 1 to 7 versus days 1 to 3; the respective percentages for severe local reactions were the same for days 1 to 7 and 1 to 3 (Table 27:).

Systemic reactions in children

During the 7-day reporting period following the first/single meningococcal vaccination, in the overall 2 to 10 years age population, across all vaccine groups, the most commonly reported systemic reaction was irritability, (range across vaccine groups, 11% to 22%), followed by: sleepiness (9% to 18%), change in eating habits (10% in all three vaccine groups), malaise (8% to 12%), headache (9% to 11%), myalgia (7% to 10%), and diarrhoea (6% to 8%, Table 29). No other systemic reaction was reported by more than 6% of the subjects in any vaccine group. The two most commonly reported systemic reactions, irritability and sleepiness, were reported by highest percentages after Menactra (22% and 18%, for irritability and sleepiness, respectively) and by lowest percentages after Menomune (11% and 9%, respectively). The reporting rates for irritability and sleepiness following administration of MenACWY (18% and 14%, respectively) were lower than those observed for Menactra but still higher than those observed for Menomune. The percentages of subjects reporting all other systemic reactions were similar across the three vaccines groups.

8.3.3. Deaths and other serious adverse events

8.3.3.1. Integrated safety analyses

Infants/Toddlers

Severe systemic AEs were experienced by similar percentage of subjects in both the MenACWY and control groups following each vaccination as shown in Figure 4, in the 4 vaccination groups. The percentages of severe AEs were low, never exceeding 1% for any solicited reaction in either dose group, except irritability after dose 1 (2%). Fever occurred in 9% of subjects after one dose and 7% after 2 doses. Fever $\geq 40^{\circ}\text{C}$ occurred in < 1% of subjects in both groups.

The percentages of catch-up subjects who experienced any AEs that were deemed severe were comparable following a first dose (6%) and after a second dose (5%). The percentages of subjects who experienced severe local AEs were low ($\leq 1\%$ following both doses), while the

percentages of subjects who experienced severe systemic AEs were again similar following a first dose (5%) and a second dose (4%).

Children

Throughout the studies, in the overall 2 to 10 years population, no more than 1% of the subjects reported SAEs across the total MenACWY and comparator Menactra and Menomune groups. Only one of the SAEs reported, an episode of febrile convulsion, experienced by a MenACWY subject in the 2 to 5 years age stratum in Study V59P10, was judged as at least possibly vaccine-related. In the pooled analysis, reports of SAEs were more frequent when two doses of meningococcal vaccine were administered in the 2 to 5 years age group (3% and 12% in the MenACWY-MenACWY and Mencevax-MenACWY groups, respectively). This was accounted for in part by the fact that the overall reporting period for the subjects receiving two vaccinations was longer compared with the reporting period for the single vaccination groups (8 to 18 months versus 6 months).

Deaths

Eleven (11) subjects died during the study period in the 7 studies included for the proposed indication in the infant/toddler group: 3 in Study V59P14 and 8 in Study V59P23. There were no deaths in the studies in the 2-10 age groups. None of the deaths were assessed as possibly or probably related to the MenACWY vaccine. The deaths were from a diversity of causes (automobile accident, lung infection, sepsis, cardiorespiratory failure, bronchopneumonia, septic shock, respiratory failure, sudden death, cardiac arrest (2), anomalous pulmonary venous connection, and head injury) and without time clustering with respect to vaccination.

8.3.4. Discontinuations due to adverse events

Overall, for the infants, 0.6% of subjects in the 4-dose MenACWY group (55/8735) and 0.5% in the 4-dose control group (15/2864) experienced unsolicited AEs that led to withdrawal from the study in which they occurred. For the catch-ups, 0.2% (3/1985) of subjects in the 2-dose group experienced AEs that led to withdrawal from the study in which they occurred. In children, 2-10 years, no AEs leading to withdrawal were reported in any of the four studies.

8.4. Evaluation of issues with possible regulatory impact

8.4.1. Liver function and liver toxicity

N/A

8.4.2. Renal function and renal toxicity

N/A

8.4.3. Other clinical chemistry

N/A

8.4.4. Haematology and haematological toxicity

N/A

8.4.5. Other laboratory tests

N/A

8.4.6. Electrocardiograph findings and cardiovascular safety

N/A

8.4.7. Vital signs and clinical examination findings

N/A

8.4.8. Immunogenicity and immunological events

8.4.8.1. Integrated safety analyses

Kawasaki Disease

In total, 7 cases of Kawasaki disease have been reported from studies in the MenACWY program. Six (6) cases occurred in recipients of MenACWY (in 5 cases routine childhood vaccines had been administered at the same time). One case occurred in a control subject (who received only routine childhood vaccines). Six (6) of these cases occurred in infants/toddlers while one case occurred in a 3-year-old child vaccinated with an earlier formulation of MenACWY that included an adjuvant from Study V59P7. Five of the infant/toddler cases were considered possibly related to MenACWY by the investigator as they occurred within 30 days after the vaccination. The remaining 2 infant or toddler cases remain designated as not related to the study vaccine due to an onset ~3 months after MenACWY vaccination.

Incidence rates of KD

Annual incidence rates of Kawasaki disease (KD) per 100,000 children < 1 year of age have not been reported in publications or other publicly available documents for other vaccines. Therefore, estimates of KD incidence rates were calculated based on study group size and follow-up time for the pre-licensure for the Rotarix, Rotateq, and Prevnar Phase III clinical trials (as an analogous group). Novartis calculated overall annual KD incidence rates per 100,000 children as 88, 18, and 49 per 100,000 children for the Rotarix, Rotateq, and Prevnar Phase III clinical trials, respectively. The annual KD incidence rates for the treatment arms of these studies ranged from 30 to 111 per 100,000 and the control arms ranged from 6 to 63 per 100,000. Except for the placebo arm of the Rotateq trial, all of the incidence rates are higher than the generally reported rates reported for this age group in the U.S. and selected European countries (approximately 20 per 100,000), but similar to those calculated for infant MenACWY subject.

Based on cumulative 15,776 subject-years of surveillance for all MenACWY studies in children up to the age of 5, the estimated annual incidence of KD is 32 (95% CI: [10, 74]) per 100,000 children (5 confirmed cases in MenACWY treatment arms in 15,776 subject-years of surveillance). In comparison, the estimated annual incidence rate for the confirmed KD case in the control arms, based on 4,722 subject-years of surveillance for all studies, is 21 (95% CI: [0.5, 118]) per 100,000 children. The estimated relative risk is 1.5 (95% CI: [0.17, 70.78]); showing no statistically significant difference between the treatment arms.

8.4.8.2. Main/pivotal studies that assessed safety as the sole primary outcome

N/A

8.4.8.3. Pivotal and/or main efficacy studies

N/A

8.4.8.4. Other studies

N/A

8.4.9. Serious skin reactions

N/A

8.4.10. Other safety parameters

N/A

8.5. Other safety issues

N/A

8.6. Post marketing experience

There are 4 post-marketing studies completed, reports submitted late (April 2017). These are briefly summarised below.

8.6.1. V59_36

This was a Phase IIIb, open-label, randomised, multicentre study carried out in 2010-2012, to assess the immunogenicity of a 3-dose vaccination schedule (2, 4 and 12 months of age) of MenACWY vaccine compared to a 4-dose vaccination schedule (2, 4, 6 and 12 months of age) and to evaluate non-inferiority of PCV-13 vaccine co-administered with ACWY and routine vaccines to those co-administered with routine vaccines only. The first primary objective of demonstrating a sufficient immune response in terms of percentages of subjects with hSBA $\geq 1:8$ against meningococcal serogroups A, C, W and Y 1 month after a 4-dose MenACWY vaccination series at 2, 4, 6 and 12 months of age was met. Similarly, the second primary objective of demonstrating non-inferiority of the immune response of a 3-dose MenACWY vaccination series (ACWY3 group) compared to a 4-dose series (ACWY4) as measured by percentages of subjects with hSBA $\geq 1:8$ at 13 months of age against meningococcal serogroups C, W and Y was also achieved.

The study also characterised the kinetics of immune response following the first, second and third infant doses. While there was a small increase from baseline values (only against serogroups C and W) following the first vaccination, a robust immune response was observed following the second and third vaccinations against all serogroups. Prior to the toddler vaccination at 12 months, the percentages of subjects with hSBA $\geq 1:8$ against all serogroups were higher in ACWY4 than in ACWY3. The bactericidal antibody levels in both groups were higher than those of subjects who received only routine vaccinations, with the exception of serogroup A in the ACWY3 group.

8.6.1.1. Results

Following the toddler vaccination, robust immune responses were observed in both ACWY3 and ACWY4 in terms of hSBA GMTs and percentages of subjects with a 4-fold rise in hSBA titres from pre-toddler dose values, against all 4 serogroups. Non-inferiority of the immune response to PCV-13 antigens, for subjects who received a 3- or 4-dose MenACWY vaccination series in co-administration with PCV-13 and routine vaccines compared to subjects who received PCV-13 and routine vaccinations only, was assessed as a secondary objective. The overall power to demonstrate non-inferiority for Family 2 serotypes was however low (43%), as the study had not been initially powered for this comparison. At 13 months of age, immune responses in the ACWY4 and ACWY3 groups were non-inferior to responses in the Routine group against all 13 pneumococcal serotypes following completion of a 4-dose PCV-13 series, although at 7 months of age, after infant vaccination series, the lower limit of the 2-sided 95% CI for the group difference of percentage of subjects with anti-pneumococcal antibodies $\geq 0.35\mu\text{g/mL}$ was greater than the prespecified margin of -10% for 11 of 13 serotypes in ACWY3 group (except serotypes 3 and 5) and for 12 of 13 serotypes in group ACWY4 (except serotype 19A).

The safety profiles of subjects in all 3 study groups were comparable and similar to previous studies. The majority of subjects reported solicited AEs, with frequencies decreasing following each subsequent infant vaccination. Systemic AEs of severe intensity following any vaccination occurred in a similar percentage of subjects administered MenACWY with concomitant vaccines compared to subjects that received routine concomitant vaccinations alone.

Overall, the most commonly reported solicited local AE was tenderness, and the most commonly reported systemic AE was irritability. The majority of solicited AEs were mild or moderate in nature. Patterns of reactogenicity recorded within 30 minutes postvaccination, from 6 hours postvaccination to Day 4, and from Day 4 to Day 7 for any vaccination were similar to what was reported in the overall 7-day reporting period. There were no appreciable differences in

percentages of reported AEs between subjects who received MenACWY and those who received routine vaccines alone.

Overall, 5% to 8% of subjects across study groups reported at least 1 SAE during the entire study period. None of the reported SAEs were judged to be related to the study vaccination. A single subject from the Routine group experienced an unrelated SAE of anoxic encephalopathy that led to death, 48 days after the first vaccination visit. No safety concerns were identified in this study.

8.6.2. Study V59_57

A Phase IIIb, randomised, observer-blind, placebo-controlled multicentre study comparing immunogenicity, safety and 1 year persistence of antibodies after either one or two doses MenACWY administered to 708 healthy children 2 to 10 years of age. This was conducted at 22 sites in the US and was commenced in October 2012. The primary objective was to demonstrate non-inferiority of 2 doses (given 2 months apart) versus 1 dose of MenACWY vaccine, by age group (2 to 5 years of age; 6 to 10 years of age), as measured by the percentage of subjects with hSBA seroresponse¹ directed against *N meningitidis* serogroups A, C, W and Y, at 1 month after last vaccination. Hence there were 4 study groups. The secondary objective was to demonstrate superiority of 2 doses (given 2 months apart) versus 1 dose of MenACWY vaccine, by age group (2 to 5 years of age; 6 to 10 years of age), as measured by the percentage of subjects with hSBA seroresponse¹ directed against *N meningitidis* serogroups A, C, W and Y, at 1 month after last vaccination. The study was considered a success if non-inferiority (for all 4 serogroups) and superiority (for at least 2 serogroups) of 2 doses versus 1 dose were demonstrated, in at least 1 age-group (2-5 years or 6-10 years). In order to achieve balance of vaccine assignment within each age cohort and site, stratified randomisation was used.

8.6.2.1. Results

A total of 715 subjects were enrolled in the study, 359 in the 2 through 5 years cohort and 356 in the 6 through 10 years cohort. The FAS included 90% of enrolled subjects in either vaccine group in the 2 through 5 years cohort and 93%-96% of subjects in the 6 through 10 years age cohort. The PPS included 77%-79% of enrolled subjects in the 2 through 5 years cohort and 81%-85% of subjects in the 6 through 10 years age cohort. The demographic and baseline characteristics of subjects were relatively balanced between vaccine groups within each age cohort and also between age cohorts. Nearly all (99% to 100% across vaccine groups and age cohorts) subjects received study vaccination, and provided postvaccination safety data and were included in the safety set.

This primary analysis compared immunogenicity and safety of 1 or 2 vaccinations of MenACWY vaccine in children 2 through 5 and 6 through 10 years of age. The primary objective of the study was to assess non-inferiority of the 2-vaccination schedule compared with the 1-vaccination schedule, followed by a superiority assessment between the same schedules. Non-inferiority of the 2-vaccination schedule to the 1-vaccination schedule was demonstrated against all 4 serogroups in both age cohorts, as the lower limit of the 2-sided 97.5% CI for the difference in seroresponse rate between the groups was greater than -10%. The superiority assessment was performed sequentially, with initial testing for serogroups C and Y, followed by assessment of serogroups A and W only if superiority could be demonstrated for serogroups C and/or Y. In the younger cohort of subjects (2 through 5 years), superiority of the 2-vaccination schedule was demonstrated for serogroups C and Y, but not for A and W. In the older cohort of subjects (6 through 10 years), superiority could only be demonstrated for serogroup Y. At 1 month after last vaccination, both the 1-vaccination and the 2-vaccination schedules resulted in substantially increased antibody levels against all serogroups in both age cohorts, compared with baseline values. Antibody responses were generally higher after 2 doses of MenACWY-CRM in younger subjects (2 through 5 years) against serogroups C and Y (nearly 5- to 7-fold higher GMTs), and to a lesser degree against serogroups A and W (nearly 2- to 3-fold higher GMTs). In

older subjects (6 through 10 years), the magnitude of the difference between the vaccine groups was not as high as in the younger age cohort.

Safety was assessed in terms of solicited and unsolicited AEs. The rates of reporting of tenderness, solicited systemic AEs, and unsolicited AEs were relatively similar after each vaccination, in both vaccine groups, in younger subjects (2 through 5 years). In the 6 through 10 years cohort, greater percentages of subjects given 2 doses of MenACWY reported pain and solicited systemic AEs after both vaccinations. Severe local or systemic AEs were reported by few subjects across vaccine groups. Possibly related unsolicited AEs were reported by greater percentages of subjects after the first vaccination in those given the 2-dose vaccination schedule. There were no deaths reported. One subject reported an SAE of petit mal epilepsy which was considered not related to study vaccination. No major safety concerns were identified in this study. Overall, the 2-vaccination schedule was shown to be non-inferior to a schedule with a single vaccination, while superiority of 2 doses to 1 dose was seen in younger children against 2 serogroups (C and Y).

8.6.3. Study V59_340B

This was a Phase IV study to assess the safety of MenACWY vaccine being used by HMO subjects aged 11-21 years of age. Data collection included the identification of all MenACWY vaccinations administered to those between the ages of 11-21 years as well as the identification and chart review (if necessary) of events of interest (EOIs) during the observation period for each vaccinee, started on September 30, 2011. The observation period for all subjects was completed by June 30th, 2014; final data collection including additional chart. The primary aim was to measure the relative incidence (RI) of a predefined set of Events of Interest (EOI) in a population exposed to MenACWY. The secondary aim was to measure the absolute incidence rate (IR) of a pre-defined set of EOIs in a population of MenACWY-CRM recipients. This was done using a retrospective analysis of the electronic medical record (EMR) databases of Kaiser Permanente Southern California (KPSC), occurrence of the EOIs was assessed during a one-year observation period following index vaccination to determine the RI of EOIs using the self-controlled case series (SCCS) method.

The specific inclusion criteria for the analysis population were:

1. Enrolled at KPSC for at least 6 months prior to MenACWY-CRM vaccination;
2. Aged 11 through 21 years (inclusive that is, has not reached their 22nd birthday) at the time of MenACWY vaccination; and
3. Received MenACWY vaccine during the study period at one of three participating centres.

For the primary and secondary objective analyses of each EOI, subjects with a pre-existing condition of that EOI were excluded. There were in total 55,397 subjects 11-21 years of age who received MenACWY between September 30, 2011 and June 30, 2013. Among those, 48,899 subjects had at least 6 months HMO membership prior to MenACWY index vaccination. All EOIs that occurred during the 1 year observation period following the index MenACWY vaccination were assessed retrospectively.

8.6.3.1. Results

A total of 55,397 persons aged 11-21 years, seen at one of three participating medical centres, were vaccinated with MenACWY-CRM during the study period. Of these, 48,899 had at least 6 months membership prior to MenACWY-CRM index vaccination and were included in the analysis population. Following the exclusion of pre-existing cases and cases refuted by the CRC, a total of 1,127 cases among the 26 pre-specified EOIs were identified for analyses. Of these, 260 cases occurred in the risk windows and 867 occurred in the comparison windows following index vaccination. There were insufficient cases for most of the EOIs (17 out of 25 pre-specified EOIs; meningococcal disease excluded) to detect a RI of at least 10 with 90% power in the SCCS analysis. Four EOIs (new onset juvenile diabetes mellitus, new onset asthma, allergic urticaria

and suicide attempt) had no statistically increased RI. In the analysis adjusted for seasonality, the initial adjusted RIs based on cases identified through the automated search algorithm for seizure (RI: 2.9, 95% CI: 1.5-5.9), iridocyclitis (uveitis) (RI: 3.1, 95% CI: 1.1-8.7), and Hashimoto's disease (RI: 5.5, 95% CI: 2.3-13.3) were statistically significant. However, following physician co-investigator chart review, the risk was no longer increased due to refutation of diagnosis or revision of date of onset, or could be explained by causes other than vaccination. There was a statistically significant increased RI for Bell's palsy (RI: 2.9, 95% CI: 1.1-7.5; 8 cases in the risk window and 10 cases in the comparison window). Stratified analyses indicated the increased risk was driven by subjects receiving concomitant vaccines (RI: 5.0, 95% CI: 1.4-17.8), with cases in the risk window occurring 5-10 weeks post vaccination. The highest overall incidence estimates (per 100,000 person-years) during the risk window were detected for new onset asthma (IR: 2206.5/100,000 person-years; 95% CI: 1924.8-2529.3), followed by suicide attempt (IR: 162.1/100,000 person-years; 95% CI: 84.3-311.5), and allergic urticaria (IR: 102.5/100,000 person-years; 95% CI: 25.6-409.9).

Several EOIs demonstrated statistically significant elevated risk in adjusted SCCS analyses. However, with the exception of Bell's palsy, following medical chart review by the physician co-investigator, risk signals either disappeared due to refutation of cases or revision of the onset date to be outside of the risk window, or could be explained by other likely medical causes. The study found an increased risk of Bell's palsy in 84 days following MenACWY vaccination, although the increase was mainly found if other vaccines were given concomitantly with MenACWY. No independent assessment is available. All Bell's palsy cases resolved completely in a short period of time with no long term consequences.

8.6.4. V59_540B

This was a post-licensure observational safety surveillance study of MenACWY vaccination in children 2 through 10 years of age. It was conducted to summarise the occurrence of serious medically attended events and 26 pre-specified events of interest (EOI) occurring up to 1 year after vaccination with MenACWY in children 2 through 10 years of age in a routine clinical care health maintenance organisation (HMO) (conducted at 3 medical centres, same setting as P59_340B). This was a retrospective descriptive observational safety surveillance study among persons 2 to 10 years of age who received the vaccine as part of their routine clinical care. The electronic medical record (EMR) databases were retrospectively analysed to detect the occurrence of incident serious medically attended events or EOIs during an observation period up to one year following the index vaccination (first dose of MenACWY). For each individual, the observation period during which the first event of each serious medically attended event or EOI was captured was up to 1 year following the index vaccination, disenrollment, or until April 1st, 2015, whichever came first.

There were in total 387 children 2-10 years of age who received MenACWY between September 30, 2011 and September 30, 2014. Among those, 327 subjects had at least 6 months of health maintenance organization records prior to their MenACWY index vaccination.

Baseline characteristics of the study population: the mean age at index MenACWY vaccination was 7.9 years (standard deviation (SD): 2.7 years), and the median age at index vaccination was 9 years. The majority of subjects (72.2%; n=236) received their index vaccination between 7 to 10 years of age. About 80.1% (n=262) of subjects received one (31.2%, n=102) or more (48.9%, n=160) other vaccines concomitantly with the index MenACWY vaccination, mostly tetanus, diphtheria, and acellular pertussis (42.2%, n=138), typhoid (25.7%, n=84), influenza (20.5%, n=67) and human papillomavirus (19.9%, n=65). For the majority (97.9%, n=320) of subjects, the index MenACWY vaccination was a primary series dose and for 7 (2.1%) subjects, a booster dose. There were 311 (95.1%) subjects who received MenACWY as the first dose of the primary series. A total of 7 subjects received the first and second doses of the primary series during the study period.

8.6.4.1. Results

Of the 327 subjects included in the analysis population, a total of 268 (82.0%) persons were followed for the entire 1-year observation period. There were 43 (13.1%) subjects who did not complete the entire 1-year observation period due to disenrollment from the HMO. There were 21 subjects who experienced at least one new onset serious medically attended event during the observation period (18 subjects experienced multiple events). Among these 21 subjects, 19 subjects (90.5%) had received a primary series dose (18 with a primary series first dose, 1 with a primary series second dose) as the index vaccination and 13 (61.9%) had received at least one concomitant. The highest incidence rate was for 'Injury and poisoning' (n=7, IR=41.4 cases per 1000 person-years, 95% CI: 19.7 - 86.8 per 1000 person-years). This was the only event class with sufficient numbers (that is, ≥ 5 events) to calculate an incidence rate. Medical chart review found that all 7 cases were due to trauma with a median time to event of 133 days (min-max range: 33-343), and were not likely vaccine related.

Among the 327 subjects in the analysis population, one new onset asthma case was confirmed as an EOI, however with very late onset. The chart review of all injury and poisoning cases demonstrated that none were likely vaccine-related. The primary limitation of this study is the small sample size of the analysis population.

8.7. Evaluator's overall conclusions on clinical 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 post-vaccination; 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.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

Indication	
Benefits	Strengths and Uncertainties
<p><i>Prevention of invasive meningococcal disease in infants (<2) and children 2-10 years.</i></p> <p><i>Acceptable safety profile</i></p>	<p><i>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 $\geq 1:8$ for all serogroups using a validated bactericidal antibody assay after a 4-dose series beginning from 2</i></p>

Indication	
Benefits	Strengths and Uncertainties
	<p><i>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.</i></p> <p><i>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).</i></p> <p><i>In children, aged 2-10 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.</i></p> <p><i>Statistical definition of non-inferiority was not met in the 2-5 and 6-10 age groups for serogroup A, when compared to Menactra but was seen in the overall 2-10 age group.</i></p> <p><i>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 (our second commonest serogroup) ²and 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.</i></p> <p><i>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).</i></p> <p><i>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.</i></p>

² According to the Invasive Meningococcal Disease National Surveillance Report published in 2017 serogroup W followed by B, and Y are now the most common in Australia.

9.2. First round assessment of risks

Risks	Strengths and Uncertainties
<p><i>Statistically higher responses followed MenACWY compared with Menactra for serogroups W and Y, C was non-inferior but in the groups 2-5 and 6-10, the response to serogroup A was inferior (but not when the groups were combined).</i></p> <p><i>Unexpected serious adverse events, in particular Kawasaki disease were identified in 5 children who received MenACWY (within 30 days).</i></p>	<p><i>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.</i></p> <p><i>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.</i></p>

9.3. First round assessment of benefit-risk balance

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

10. First round recommendation regarding authorisation

The evaluator recommends 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.

11. First round recommendation regarding authorisation

[Insert all information]

12. Clinical questions

No questions were raised by the evaluator.

13. 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 in the AusPAR).

14. References

Nil

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