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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Menveo

(MENINGOCOCCAL GROUP A, C, W135 AND Y CONJUGATE VACCINE)

Procedure no. EMEA/H/C/001095/II/0018

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Ad+	With aluminum phosphate adjuvant
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CRM197	Cross Reactive Material, a nontoxic mutant of diphtheria toxin
CSR	Clinical Study Report
DTaP-HBV-IPV Pediarix	combined diphtheria and tetanus toxoids, acellular pertussis adsorbed, hepatitis B (recombinant) and inactivated poliovirus vaccine
EC	European Commission
ELISA	Enzyme Linked Immunosorbent Assay
EU	European Union
FHA	Filamentous hemagglutinin
GCP	Good Clinical Practice
GMC	Geometric mean concentration
GMP	Good Manufacturing Practice
GMR	Geometric mean ratio
GMT	Geometric mean titer
HAV Havrix	hepatitis A vaccine
HBV	Hepatitis B vaccine
Hib ActHIB	(haemophilus b conjugate vaccine [Tetanus Toxoid Conjugate])
hSBA	Serum bactericidal assay using human complement
ICH	International Conference on Harmonisation
IM	Intramuscular
IPV	Inactivated poliovirus vaccine: poliovirus types 1, 2, and 3
IU	International Unit
LL	Lower Limit
m	month(s)
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MenC	Monovalent meningococcal serogroup C CRM197 conjugate vaccine Menjugate
MITT	Modified Intention-to-Treat
MMRV	Mumps, measles, rubella, varicella vaccine
PCV7	Heptavalent pneumococcal conjugate vaccine
PDCO	Paediatric Committee
PIP	Paediatric Investigation Plan
PP	Per Protocol
PRN	Pertactin
PT	Pertussis toxin
RCDF	Reverse Cumulative Distribution Function

rSBA	Serum bactericidal assay using rabbit complement
SC	Subcutaneous
SD	Standard deviation
Tdap	Tetanus, Diphtheria, acellular Pertussis
US	United States of America

1. Scientific discussion

1.1. Introduction

Menveo is a quadrivalent meningococcal conjugate vaccine containing serogroups A, C, W135, and Y (henceforth referred to as MenACWY). MenACWY uses pre-sized oligosaccharides from each of the primary pathogenic serogroups (A, C, W135, and Y) conjugated to the CRM_{197} protein carrier. The final formulation contains 10-5-5-5 µg per oligosaccharide of *N. meningitidis* serogroups A, C, W, and Y respectively, without an adjuvant.

MenACWY is currently indicated for active immunization of children, adolescents (from 2 years of age) and adults at risk of exposure to *Neisseria meningitidis* groups A, C, W135 and Y, to prevent invasive disease. The use of this vaccine should be in accordance with official recommendations.

The vaccine is presented in the form of one vial containing the lyophilised MenA conjugate component plus excipients, and one syringe or one vial containing the liquid MenCWY conjugate component plus excipients. The pharmaceutical form is powder and solution for solution for injection. An additional immediate packaging for MenCWY liquid finished product (3mL glass vial with a 13 mm stopper and flip-off) in addition to the approved syringe was approved in March 2011.

A number of Scientific Advices were held with EMA to discuss the clinical development of Menveo, including the development in infants from 2-23 months of age. In May 2009 the latest Scientific Advice was received from CHMP (EMEA/CHMP/SAWP/288055/2009). The main outcomes for the clinical program in this population were:

1. The safety database was considered acceptable in accordance with the guideline on clinical evaluation of new vaccines.
2. The overall primary endpoint hSBA titre of >1:8 should be considered for initially seronegative subjects, whereas a fourfold rise in hSBA titre should be considered as primary endpoint for initially seropositive subjects. Novartis agreed to the pre-existing immunity in the evaluation of seroresponses in subjects 2 years and above but not infants and toddlers for which Novartis argued that pre-existing antibodies measured using the hSBA were either of maternal origin (in infants at 2 months of age) or non-existing (in older infants and toddlers). For this younger age group, this approach was also taken to align with requests from other regulatory agencies.
3. CHMP recommended using an active comparison with MenC Conjugate vaccine in this age group. Accordingly, a new EU infant/toddler study (V59P22) was included in the Menveo clinical program. The revised proposed program in subjects below 2 years of age was considered acceptable.
4. Previously, it was also indicated that at 12 months of age rapid waning of bactericidal antibodies was considered a major concern and was requested to be addressed in the infant program. This evaluation of the persistence of bactericidal antibodies is ongoing and is an integral part of the Menveo clinical development program as well as an assessment of the need for, and timing of, a booster dose.

1.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

1.3. Clinical aspects

1.3.1. Introduction

GCP

The MAH stated that trials were performed with the ethical principles that are consistent with Good Clinical Practice (GCP) and according to the International Conference on Harmonisation (ICH) guidelines. The MAH has also provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

In May 2012 the CHMP was informed of GCP issues identified for one study site included in study V59P22. An updated Clinical Study Report was submitted in June 2012. The safety data collected at one site was not in line with expectations as only very few adverse events were reported. Moreover, diary cards appeared unused. The outcome of an EMA inspection (for different study and investigational product, study V70P5) was that use of the data from that site was not recommended. Consequently, the MAH decided to exclude all data from the affected site from the analysis in the study report also for study V59P22.

Further to this, the MAH informed CHMP in November 2012 of further GCP issues with a site participating in the other three phase III studies included in this submission (V59P14, V59P21, V59P23). The problems concerned the source documentation and that specifically the rates of diary card return & recall were 'much lower' than what was communicated verbally during the study. This concerned the reporting of reactogenicity alone and the reporting of unsolicited adverse events was not affected, according to the MAH. As a result the MAH decided to remove information on solicited adverse events from this site from the analyses.

The MAH confirmed that all study sites in the present submission were monitored for GCP compliance. In addition, internal audits took place in line with the audit program and audit certificates were provided as part of the submission. Based on these activities, the MAH confirmed that other than the instances noted to EMA or in the Clinical Study Reports, the studies were conducted in compliance with GCP.

Table 1. Tabular overview of clinical studies

Study ID	Geo-graphic Location	Study Objective (Primary)	Design	Test Product(s); Dosage Regimen; Route of Administration	Subjects by arm	Age groups included	GCP Issues
PHASE II STUDIES							
V59P2	Finland Germany	Safety & Immunogenicity Dose Ranging Study	Observer-Blind, Randomized, Active Controlled, Phase 2, Multi-Centre	• MenACWY 10-10-10-10µg Ad+ IM • MenACWY 0-10-10-10 µg Ad+ IM • MenACWY 10-5-5-5 µg Ad+ IM • MenACWY 5-5-5-5 µg Ad+ IM • MenACWY 2.5-2.5-2.5-2.5µg Ad+ IM • Menjugate IM	• 109 • 106 • 103 • 101 • 104 • 97	Toddlers (12-16 months)	
V59P4	US	Safety & Immunogenicity Dose Ranging; Men ACWY with & without Adjuvant vs. Menomune	Double-Blind, Randomized, Active Controlled Phase 2 Multi-Centre	• MenACWY10-10-10-10µg Ad- IM • MenACWY5-5-5-5µg Ad-IM • MenACWY5-5-5-5 µg Ad+ IM • Menomune SC	• 81 • 79 • 75 • 80	Toddlers (12-16months): MenACWY Children (3-5 years): Menomune	
V59P5	UK Canada	Safety & Immunogenicity Schedule Finding Two or Three Doses With Concomitant Infant Routine Vaccinations Persistence of Antibodies, Booster and Memory Response	Open-label, Randomized, Active Controlled Phase 2 Multi-Centre	• MenACWY+ & MenACWY+ Boost IM • MenACWY+ & no Boost IM • MenACWY+ followed by 1/5th Dose Menomune SC • MenACWY- & 10-5-5-5 µg Ad- Boost IM • MenACWY- followed by 1/5th Dose Menomune SC • Menjugate & MenACWY+ Boost IM	• 229 • 49 • 98 • 135 • 45 • 45	Infants (2 months)	

V59P7	Finland Poland	Safety & Immune Response of MenACWY with and without Adjuvant vs. Mencevax	Observer Blind, Randomized, Active Controlled Phase 2 Multi-Centre	• MenACWY10-5-5-5 µg Ad+ IM • MenACWY10-5-5-5 µg Ad– IM • Mencevax IM followed by MenACWY10-5-5-5 µg Ad– IM	• 205 • 331 • 81	Toddlers (12-35 months) Children (36-59 months)	
V59P8	US	Safety & Immune Response of MenACWY vs. Menomune	Single-Blind, Randomized, Active Controlled in Children Open-Label in Toddlers Phase 2 Single-Centre	• MenACWY • MenACWY (+PnC) • MenACWY (+ DTaP) • Menomune SC	• 453 • 71 • 73 • 310	Children (2-10 years) Toddlers (12-23 months)	
V59P9	Canada	Schedule Finding Safety & Immune Response After One or Two Doses of MenACWY	Open Label, Partially Randomized, Active Controlled Phase 2 Multi-Centre	• MenACWY • Menjugate followed by MenACWY	• 125 • 50	Infants (6 -12 months)	
V59P16 Non-IND Study	UK	Safety & Immunogenicity Memory B Cell Response to MenACWY at 2, 4 and months of age	Open-Label, Randomized Phase 2 Single-Centre	• MenACWY	• 216	Infants (2 months)	
PHASE III STUDIES							
V59P14	US Argentina Colombia	Safety & Immune Response of MenACWY given with US Routine Infant Vaccines Followed by MenACWY Booster vs. Routine Infant	Open-Label, Randomized, Phase 3 Multi-Centre	• MenACWY (+ Routine Vaccines) • Routine Vaccines Only Followed by MenACWY	• 3022 • 1511	Infants (2 months)	One site (informed 9-11-2012): solicited AE data from 87 subjects (1.9%) removed.

		Vaccines Alone Followed by two Doses MenACWY in 2nd Year of Life					
V59P21	US	Safety and Immune Response of MenACWY with ProQuad administered at various schedules	Open-Label, Randomized Phase 3 Multi-Centre	• MenACWY followed by MenACWY plus ProQuad SC • MenACWY followed by MenACWY IM followed by ProQuad • ProQuad SC	• 500 • 503 • 600	Infants (7-9 months)	One site (informed 9-11-2012): solicited AE data from 48 subjects (3%) removed.
V59P22	Germany	Safety and Immune Response of One or Two Doses of MenACWY vs. Menjugate	Open-Label, Randomized Active Controlled Phase 3 Multi-Centre	• MenACWY 2x • MenACWY • Menjugate IM	• 196 • 205 • 193	Infants (12 months)	One site (Data excluded in CSR, initially 219, 228 & 215 subjects were enrolled)
V59P23	US, Taiwan, Costa Rica, Guatemala, Peru and Panama	Safety of MenACWY plus routine vaccines vs routine vaccines alone at 2, 4, 6, and 12 months of age	Open-Label, Randomized Active Controlled Phase 3b Multi-Centre	• MenACWY + routine vaccines • Routine vaccines only	• 5775 • 1925	Infants (2 months)	One site (informed 9-11-2012): solicited AE data from 5 subjects (0.3%) removed.

1.3.2. Clinical efficacy

1.3.2.1. Dose response studies

The dose-response studies were submitted and assessed with the initial MAA. A short summary of the main findings is provided below.

Studies V59P2, V59P4, V59P7

The selection of the MenACWY 10-5-5-5 dose was based on the results of study V59P2. This study planned to enrol 600 toddlers aged 12 to 16 months into one of six vaccination groups. Four groups received one injection of aluminium phosphate-adjuvanted MenACWY with the dose of each serogroup ranging from 2.5 µg to 10 µg. Based on preclinical data indicating the possibility of interference between the serogroup A antigen and the other serogroups, the study included a fifth group, which was administered MenCWY containing 10 µg of three serogroups C, W, and Y (MenCWY 10-10-10), while the control group was administered monovalent meningococcal serogroup C CRM197 conjugate vaccine Menjugate (MenC). A subset received a second vaccination of the previously received dose. There was no evidence of interference or reduction in immunogenicity of the ACWY10 vaccine against any of the four serogroups by reason of the presence of the A antigen.

Study V59P4 planned to enrol 225 toddlers (aged 12 to 16 months) to evaluate the immunogenicity and safety of MenACWY 5-5-5-5 formulated with and without aluminium phosphate adjuvant and non-adjuvanted MenACWY 10-10-10-10. In addition, a licensed polysaccharide meningococcal ACWY vaccine (Menomune) was administered to a planned group of 75 children aged 3 to 5 years as an immunogenicity comparator group. hSBA geometric mean titres (GMTs) were used in study V59P4 to assess the impact of the inclusion of the adjuvant. Baseline hSBA GMTs were very low or undetectable in all groups. One month after vaccination, no statistically significant ($p > 0.05$ in each pairwise test) difference in hSBA GMTs between the non-adjuvanted and adjuvanted groups was observed. Regarding the tolerability and safety, no noteworthy differences between the adjuvanted and non-adjuvanted MenACWY vaccine were seen. Both formulations were well tolerated.

Study V59P7 planned to enrol 600 subjects: 400 children aged 12 to 35 months were to receive MenACWY 10-5-5-5 formulated with or without adjuvant and 200 subjects aged 36 to 59 months were to receive either non-adjuvanted MenACWY 10-5-5-5 or a meningococcal polysaccharide ACWY vaccine (Mencevax). All subjects were to receive a second vaccination of adjuvanted or non-adjuvanted MenACWY 10-5-5-5 at 1, 6, or 12 months after the first injection. Baseline hSBA GMTs were very low or undetectable in all groups. One month after vaccination no statistically significant difference in hSBA GMTs between the non-adjuvanted and adjuvanted groups was observed. Both MenACWY Ad+ and Ad- were well tolerated with a lower local reactogenicity profile compared to polysaccharide MenACWY. No unexpected unsolicited or otherwise clinically significant adverse events (AEs) related to the vaccines administered were reported in this study. No deaths occurred in the study.

In conclusion, the final formulation contains 10-5-5-5 µg of oligosaccharide of *N. meningitidis* serogroups A, C, W, and Y, respectively, without an adjuvant.

Study V59P5, infant dosing regimen

V59P5 was a phase 2, randomised, open label, controlled, multicenter trial conducted in the UK and Canada during 2004-2006 to assess the tolerability and immunogenicity of either 2 doses (at 2 and 4 months) or 3 doses of Menveo administered concomitantly with routine infant immunization schedules in the UK (at 2, 3, 4 months of age) and Canada (at 2, 4, 6 months of age). Additionally, subjects were evaluated for the persistence of antibodies at 12 months of age and received either no further

vaccinations, another dose of investigational meningococcal conjugate vaccine or a reduced dose (1/5th of the total quantity) of a meningococcal polysaccharide vaccine (Menomune) (MPSV4) as an "immunologic probe" for demonstration of memory. Overall, 601 subjects were enrolled in the study and received at least 1 vaccination.

Originally the formulation used in this trial was 10-5-5-5 µg with an aluminium phosphate adjuvant (Ad+). After regulatory feedback during the course of the trial, the study was amended to also include non-concurrently enrolled groups to receive the formulation 10-5-5-5 µg without adjuvant. Not all schedules were repeated with the unadjuvanted formulation (e.g., no group received the unadjuvanted final formulation vaccine at 2, 4, and 6 months of age). Ultimately, no clinically meaningful benefit was observed with inclusion of the adjuvant with similar immune responses for all serogroups when administered with the same dosing regimen. For this reason, in order to provide a complete analysis of dosing regimen selection, the text below includes discussion of study groups that received either the adjuvanted or the unadjuvanted formulation.

Immunogenicity results

The decision to pursue a dosing regimen of Menveo administration at 2, 4, 6, and 12 months of age was based on the following results from study V59P5:

- Higher percentages of infants achieved an hSBA ≥ 1:8 at one month after vaccination at 2, 4, and 6 months of age (76% for serogroup A, 98% for C, 96% for W, 89% for Y) than at one month after vaccination at 2 and 4 months of age (49% for A, 89% for C, 92% for C, and 86% for Y).
- At 12 months of age, infants who had received three doses of Menveo at 2, 4 and 6 months showed better persistence of response (hSBA 1:8: 23% for A, 65% for C, 73% for W, 77% for Y) than did those who had received 2 doses at 2 and 4 months (hSBA 1:8: 3% for A, 25% for C, 54% for W, 53% for Y).
- For both regimens, a further dose at 12 months of age boosted hSBA 1:8 responses to between 86% and 100% for all serogroups.

The 3-dose primary course thus provided more protection over the second 6 months of life than did the 2-dose regimen, where responses waned considerably, especially against the A serogroup. In both cases, a 12-month dose then boosted responses to high levels.

Study V59P5 involved more vaccine groups than described above. As previously mentioned, most of the vaccine groups in study V59P5 received MenACWY Ad+. However one group (UK 2,4-) received Menveo without adjuvant (but with polysorbate) at 2, 4 and 12 months and another group received Menjugate at the same time points. Since this study provides only one comparison between monovalent conjugated MenC vaccine and Menveo for the infant primary series these results are presented in the table below.

Table 2. Results for study V59P5 vaccine groups: UK 2,4- and Menjugate.

Time point:	**Baseline (2 m)**	**At month 5 after two doses**	**At month 12 before dose 3**	**At month 13, one month after dose 3**
Endpoint:	**% with hSBA≥1:8**			
UK 2,4- (N=69)	4	83	26	94
Menjugate (N=38)	11	97	87	97
Endpoint:	**GMT**			
UK 2,4- (N=69)	2.5	44	3.9	129
Menjugate (N=38)	2.8	343	27	912

1.3.2.2. Main studies

Three of the phase III studies were efficacy studies – V59P14, V59P21 and V59P22. Even though the specific study designs, objectives and the populations under study varied, the basic methodology for the clinical development plan for MenACWY was consistent across all studies.

Methods

Study Participants

Male and female subjects had to be in good health, born after full term pregnancy with an estimated gestational age ≥37 weeks and a birth weight ≥2.5 kg, and should not have received any prior vaccination against meningococci of groups ACWY or have any history of meningococcal infections. Age ranges in specific (immunogenicity) studies are presented in the following table:

Table 3. Age ranges included in phase III studies

Phase III study	Age range
V59P14	2 months old (55 – 89 days, inclusive)
V59P21	7 to 9 months old
V59P22	6 to 8 months old, inclusive

In study V59P14 subjects should not have received childhood vaccines under investigation (DTP, IPV, OPV, Hib, Pneumococcal) or have had previous suspected or confirmed disease caused by, or were exposed to person with laboratory confirmed infection with, infectious agents in above named vaccines. In study V59P21 subjects should have received complete primary vaccination with recommended licensed vaccines, vaccination with rotavirus vaccine Rotateq was not required for study entry. In study V59P22 subjects should have received three doses of both heptavalent conjugate pneumococcal (Prevenar) and DTaP-Hib-HBV-IPV (Infanrix-hexa) vaccines at least 30 days before study entry.

Treatments

In the different phase III studies subjects were randomised to receive MenACWY according to different dosing schedules, with different concomitant vaccines, or to receive a comparator vaccine (CRM197 conjugated monovalent meningococcal serotype C vaccine Menjugate (MenC)).

Objectives

Primary objectives for the different studies were:

V59P14:

- To assess the immunogenicity of four doses of MenACWY given to infants at 2, 4, 6 and 12 months of age as measured by the percentage of subjects with serum bactericidal activity using human complement (hSBA) ≥1:8, directed against *N. meningitidis* serogroups A, C, W and Y (US subjects, group Ia).
- 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).

V59P21:

- To compare the immune responses of measles, mumps, rubella and varicella vaccine (ProQuad) when concomitantly administered with MenACWY vaccine to that of ProQuad vaccine when given alone to healthy young children aged 12 months, as measured by seroconversion rates to measles, mumps, and rubella, as well as seroprotection rates for varicella.
- To compare the immune responses of two doses of MenACWY given to healthy young children at 7 to 9 and 12 months of age, when MenACWY is either concomitantly administered with ProQuad vaccine given at 12 months of age or when MenACWY is given alone, as measured by percentage of subjects with serum bactericidal activity using human complement (hSBA) ≥1:8 directed against *N. meningitidis* serogroups A, C, W-135, and Y.
- To assess the immunogenicity of two doses of MenACWY given to healthy young children at 7 to 9 and 12 months of age as measured by the percentage of subjects with serum bactericidal activity using hSBA ≥1:8 directed against *N. meningitidis* serogroups A, C, W-135, and Y.

V59P22:

- To assess and compare the immunogenicity of one dose of MenACWY to one dose of MenC given to healthy toddlers at 12 months of age as measured by the percentage of subjects with serum bactericidal activity using human complement (hSBA) ≥1:8 against *N. meningitidis* serogroup C.

Secondary objectives included:

- To assess the immunogenicity of childhood vaccines (incl. boosters) given concomitantly or without MenACWY (non-inferiority) or Menjugate (V59P22) at different ages.
- To assess the persistence of bactericidal antibodies (up to 6-18 months).
- To assess the immunogenicity of MenACWY vs Menjugate as measured by rSBA (GMTs, fourfold increase, % with rSBA ≥ 1:128 and rSBA ≥ 1:8).
- To assess and compare the immunogenicity of two doses of MenACWY given to infants at 6 to 8 and 12 months of age to a single dose of MenC given to toddlers at 12 months of age as measured by hSBA GMTs, percentage of subjects with hSBA ≥1:8 and hSBA ≥1:4, directed against *N. meningitidis* serogroup C.

In general, the safety objective of the different studies was to evaluate the safety and tolerability of MenACWY and concomitant vaccines in all study subjects.

Outcomes / endpoints

The following endpoints were included in the analyses of all pivotal studies conducted to support MenACWY licensure in this application:

- hSBA ≥ 1:8;
- hSBA Geometric Mean Titers (GMTs);
- Reverse Cumulative Distribution Function (RCDF) curves

Two of the pivotal studies used also 'adequacy' of immune response for estimating the immune response to the 4-dose MenACWY series in infants (V59P14) and to 2-dose series in older infants (V59P21).

Table 4. Criteria for Evaluating Immunogenicity of MenACWY in studies V59P14 and V59P21

	Endpoint	Criteria for success
V59P14	% of subjects with hSBA ≥ 1:8	Adequacy of immune response would be declared if the lower limit (LL) of the 2-sided 95% CI surrounding the proportion of subjects achieving a post-fourth dose hSBA ≥ 1:8 was ≥ 80% for serogroup A, and ≥ 85% for serogroups C, W, and Y
	Superiority of immune responses from a fourth dose of MenACWY at 12 months vs. a first dose of MenACWY at 12 months	LL of the 2-sided 95% CI surrounding the ratio hSBA GMTs is > 2 (ratio of 4-dose GMT: 1-dose GMT)
V59P21	% of subjects with hSBA ≥ 1:8	Adequacy of immune response would be declared if the lower limit (LL) of the 2-sided 95% CI surrounding the proportion of subjects achieving a post-second dose hSBA ≥ 1:8 was ≥ 65% for serogroup A, and ≥85% for serogroups C, W, and Y

RCDF curves were used in descriptive analyses to show the distribution of antibody titres across the study population.

Secondary endpoints and statistical criteria used to establish non-inferiority of concomitant infant and toddler vaccines are summarised in the following tables:

Table 5. Concomitant Vaccine Antigen Test Types and Key Secondary Immunogenicity Endpoints, study V59P14

V59P14						
Vaccine	**Test**	**Antigens**	**Threshold (infant series)**	**Endpoints**	**Threshold (toddler dose)**	**Endpoints**
Pediarix	ELISA	Diphtheria	***≥0.1 IU/mL***	***% ≥threshold***	***≥1.0 IU/mL***	***% ≥threshold***
	ELISA	Tetanus	***≥0.1 IU/mL***	***% ≥threshold***	***≥1.0 IU/mL***	***% ≥threshold***
	ELISA	PT FHA PRN	if baseline ≥LLQ, 4-fold increase over baseline; if baseline <LLQ, ≥ 4x LLQ	***GMC ratio*** and % ≥threshold	if baseline ≥LLQ, 4-fold increase over baseline; if baseline <LLQ, ≥ 4x LLQ	***GMC ratio*** and % ≥threshold
	NT	*Poliovirus type 1* *Poliovirus type 2* *Poliovirus type 3*	***≥ 1:8***	***% ≥threshold***		
	ELISA	HBV	***≥10 mIU/mL***	***% ≥threshold***		
ActHIB	ELISA	Hib (PRP)	***≥0.15 µg/mL***	***% ≥threshold***	***≥1.0 µg /mL***	***% ≥threshold***
Prevnar	ELISA	PnC 4 PnC 6B PnC 9V PnC 14 PnC 18C PnC 19F PnC 23F	***≥0.35 µg/mL***	***% ≥threshold***	≥1.0 µg/mL	***GMC ratio*** and % ≥threshold
Statistical Criteria for demonstrating non-inferiority of concomitant vaccine responses						
Infant vaccines: DTaP, Hib, HepB, IPV, PCV7 antigens, measured at 7 months			For D,T, Hib, HepB, and PCV7: Lower limit (LL) of 2-sided 95% CI surrounding difference in proportions with seroresponse between (MenACWY plus routine) vs. routine alone is > -10%; For Poliovirus 1,2,3: LL 2-sided 95% CI for difference is >-5%; For Pertussis (FHA, PT, PRN): LL 95% around ratio of ELISA GMCs is >0.67 (ratio of MenACWY+routine:routine GMCs)			
Toddler vaccines: PCV7, measured at 13 months, DTaP, Hib antigens measured at 17 months			For PCV7: LL of 2-sided 95% CI surrounding ratio of ELISA GMCs is > 0.5(ratio of MenACWY+routine:routine GMCs) For D, T, Hib, FHA, PT, PRN: LL 2-sided 95% CI around difference in % seroresponders is > -10% For D, T,Hib: LL 2-sided 95% CI for ratio of GMCs > 0.50 For Pertussis (FHA, PT, PRN): LL 2-sided 95% CI for ratio of GMCs >0.67			

LLQ = lower limit of quantification; IU: international units; ELISA: Enzyme-linked immunosorbent assay;
[a] key secondary endpoints as per V59P14 study protocol are indicated in ***bold italics***.

Table 6. Concomitant Vaccine Antigen Test Types and Key Secondary Immunogenicity Endpoints, study V59P21

V59P21					
Vaccine	**Test**	**Antigens**	**Threshold**		**Endpoints**
ProQuad	ELISA	Measles	Older Infants	≥255 mIU/mL	% ≥ threshold
	ELISA	Mumps		≥ 10 ELISA Ab units	% ≥ threshold
	ELISA	Rubella		≥10 IU/mL	% ≥ threshold
	ELISA	Varicella Seroconversion		≥1.25 gp ELISA units/mL	% ≥ threshold
	ELISA	Varicella Seroprotection		≥ 5 gp ELISA units/mL	% ≥ threshold
Statistical Criteria for demonstrating non-inferiority of concomitant vaccine responses					
Toddler vaccines: MMRV		For MMR: LL of 2-sided 95% CI of the difference in the percentage of subjects with seroconversion >-5% For V: LL of 2-sided 95% CI of the difference in the percentage of subjects with seroprotection >-10%			

Ab units =Antibody units; IU: international units; ELISA: Enzyme-linked immunosorbent assay; gpELISA: Glycoprotein-based ELISA

Table 7. Concomitant Vaccine Antigen Test Type and Response Endpoints, study V59P22

Vaccine	Serological Method	Antigen	Primary Endpoint	Secondary Endpoint
Infanrix-Hexa	ELISA	Diphtheria (D)	≥ 0.10 IU/mL	≥ 1.0 IU/mL
	ELISA	Tetanus (T)	≥ 0.10 IU/mL	≥ 1.0 IU/mL
	ELISA	PT FHA Pertactin	Vaccine response*	
	NT	Polio type 1 Polio type 2 Polio type 3	≥ 1:8	
	ELISA	Hep B (HBV)	≥ 10 mIU/mL	
	ELISA	PRP-T Hib	≥ 0.15 µg/mL	
			≥ 1.00 µg/mL	
Prevnar (Heptavalent)	ELISA	PnC 4 PnC 6B PnC 9V PnC 14 PnC 18C PnC 19F PnC 23F	≥ 0.35 µg/mL	≥ 1.0 µg/mL

* Vaccine response to PT, FHA and PRN was defined as:
- For initially seronegative subjects (pre-vaccination antibody concentrations <LLQ): post-vaccination antibody concentrations ≥ LLQ
- For initially seropositive subjects (pre-vaccination antibody concentrations ≥ LLQ): post-vaccination increase of at least two times the pre-vaccination antibody concentrations

Statistical Criteria for demonstrating non-inferiority of concomitant vaccine responses	
Infanrix-Hexa and Prevnar:	Immunogenicity of concomitant vaccine was considered non-inferior for any of the component antigens, if LL of two-sided 95% CI for the difference in % of subjects with antibody response greater than the cut-off level specified above for that antigen ($P_{\text{Concomitant Vaccine + MenACWY}} - P_{\text{Concomitant Vaccine+Menjugate}}$) was greater than -10%.

Sample size

Sample size calculations differed for each study, considering dependent on the randomisation ratio and stratification of enrolment.

Randomisation

In study V59P22 subjects were randomly assigned in a 1:1:1 ratio to one of the vaccination groups following a randomisation list.

For study V59P14 randomisation was done in a 2:1 ratio (MenACWY + routine infant vaccines: routine infant vaccines only). Within each region (US and Latin America), two randomisation lists were utilised, one for immunogenicity and one for safety. Each of the four randomisation lists was stratified by study site.

In V59P21 subjects were randomized in a 1:1 ratio to either Group I or II. Simultaneously, subjects who were 12 months old at the time of enrolment were entered into the open label Group III.

Blinding (masking)

All studies were designed as open-label studies; both the study personnel and the subject (subject's guardian(s)) knew which vaccine was being administered. The serological laboratories were blinded to study group in studies V59P21 and V59P22.

Statistical methods

Analysis Populations

In pivotal studies the analysis populations were defines as:

- All Enrolled Population: all subjects who signed an informed consent, underwent screening procedures and were randomised (V59P14, V59P21, V59P22).
- Exposed Population: all enrolled subjects who actually received a study vaccination (V59P14, V59P21, V59P22).
- Modified Intention-to-treat (MITT) Population:
  - Immune Response One Month after Vaccination at 12 Months of Age: all subjects in the ITT population who actually received a study vaccination, and provided at least one evaluable serum sample after vaccination (V59P22).
  - Antibody Persistence: all subjects in the ITT population who actually received a study vaccination, and provided at least one evaluable serum sample after vaccination, and provided an evaluable serum sample at 6-12 months after vaccination at 12 months of age (V59P22).
  - Immunogenicity – MMRV analysis: all subjects who actually received a study vaccination, provided at least one evaluable serum sample before and after vaccination, and were seronegative at baseline for any of the four antigens (V59P21).
  - Immunogenicity – MenACWY analysis: all subjects who actually received a study vaccination and provided at least one evaluable serum sample after vaccination (V59P21).
- Per-protocol (PP) Population:
  - Immune Response one Month after Vaccination at 12 Months of Age: all subjects in the MITT population who received all the relevant doses of vaccine correctly, and provided evaluable serum samples at the relevant time points, and had no major protocol deviation prior to database lock (V59P22).
  - Immunogenicity: all subjects in the MITT population, who received all the relevant doses of vaccine correctly, provided evaluable serum samples at the relevant time points, had no major protocol deviation prior to database lock (V59P14). For study V59P21 subjects also had to be seronegative at baseline for any of the four antigens (MMRV analyses only).
  - Antibody Persistence: all subjects in the MITT population, who received all the relevant doses of vaccine correctly, provided evaluable serum samples relevant time point, and had no major protocol deviation prior to database lock (V59P22).
- Safety population: all subjects in the exposed population who provided post-baseline safety data. If a subject received an entirely wrong vaccine schedule, the subject was to be analysed for safety according to the group the subject actually followed.

All immunogenicity analyses in this application were performed on the per protocol (PP) population.

Comparisons (please also see section on endpoints)

The primary criteria for immunogenicity in study V59P22 was that the lower limit of the two-sided 95% confidence interval (CI) was greater than -10% for the difference between one dose of MenACWY and Menjugate, as measured by the percentage of subjects with hSBA ≥1:8 for serogroup C at 1 month following the vaccination at 12 months of age (Group II vs. Group III).

The GMTs, GMRs, two-sided 95% CIs, and median, minimum and maximum values were calculated for each vaccine group within each serogroup. The GMTs, GMRs and two-sided 95% CIs were constructed by exponentiation (base 10) of the least square means of the logarithmically transformed (base 10) titres and their 95% CIs obtained from a two-way Analysis of Variance (ANOVA) with vaccination group and study centre as factors. Titres below the limit of detection were set to half that limit for the purposes of the analysis.

In study V59P14 the percentage of subjects with hSBA ≥1:8 and associated two-sided 95% confidence intervals (CIs) were computed for each serogroup in US1A. The criterion for assessment was the lower limit of the two-sided 95% CI be greater than or equal to 80%, 85%, 85% and 85% for MenA, MenC, MenW and MenY, respectively. The second primary criteria for immunogenicity was that the lower limit of the two-sided 95% CI for the ratio of the GMT of a fourth dose at 12 months of age after receiving MenACWY at 2, 4, and 6 months of age compared to the GMT of a single dose at 12 months of age (GMTUS1A / GMTUS2) is ≥ 2.0.

In study V59P21 the immune response to measles, mumps, rubella and varicella at six weeks following vaccination with one dose of MMRV given concomitantly with MenACWY was considered 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 was greater than -5% for measles, mumps and rubella and was greater than –10% for varicella (Group I vs. Group III). The immune response of MenACWY given concomitantly with MMRV (Group I) was 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≥1:8 at 6 weeks after the second dose of MenACWY given to 12-month old toddlers was greater than -10% for each serogroup (Group I vs. Group II at Visit 4).

To show adequacy of immune response for the two-dose MenACWY series, the lower limit of the two-sided 95% CI for the percentage of subjects with hSBA ≥1:8 at 6 weeks following the second dose of MenACWY needed to be greater than 85% for serogroups C, W, or Y and greater than 65% for serogroup A.

Results

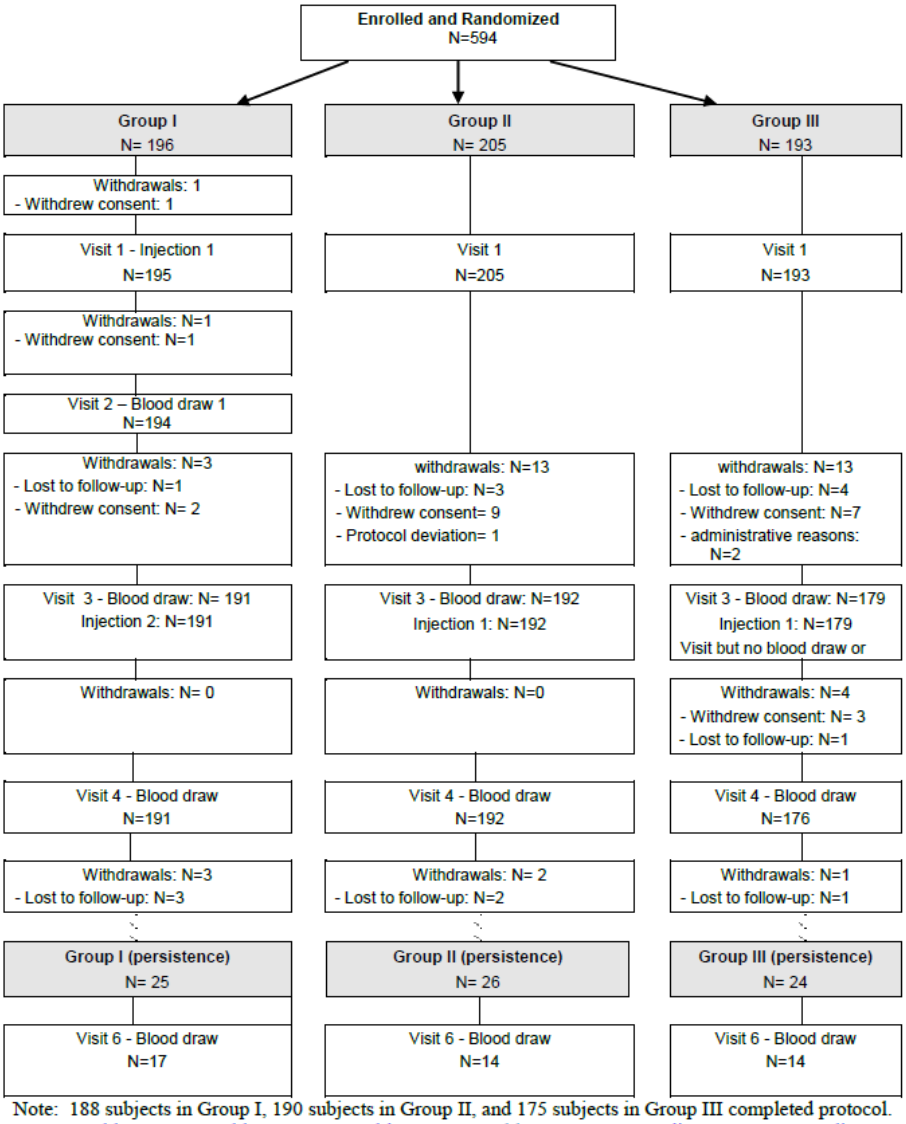
Participant flow, conduct of study, recruitment, baseline data and numbers analysed are presented below per study. The main outcomes are presented and discussed according to the following topics: Comparative immunogenicity vs Menjugate; Immunogenicity of MenACWY following different schedules; interaction with childhood vaccines; persistence of antibodies. Studies are presented in order of their relevance: V59P22, V59P14 and V59P21.

Participant flow

Study V59P22

Figure 1. Subject disposition in study V59P22

Figure 10.1-1 Subject Disposition – Enrolled Population Excluding Site 18



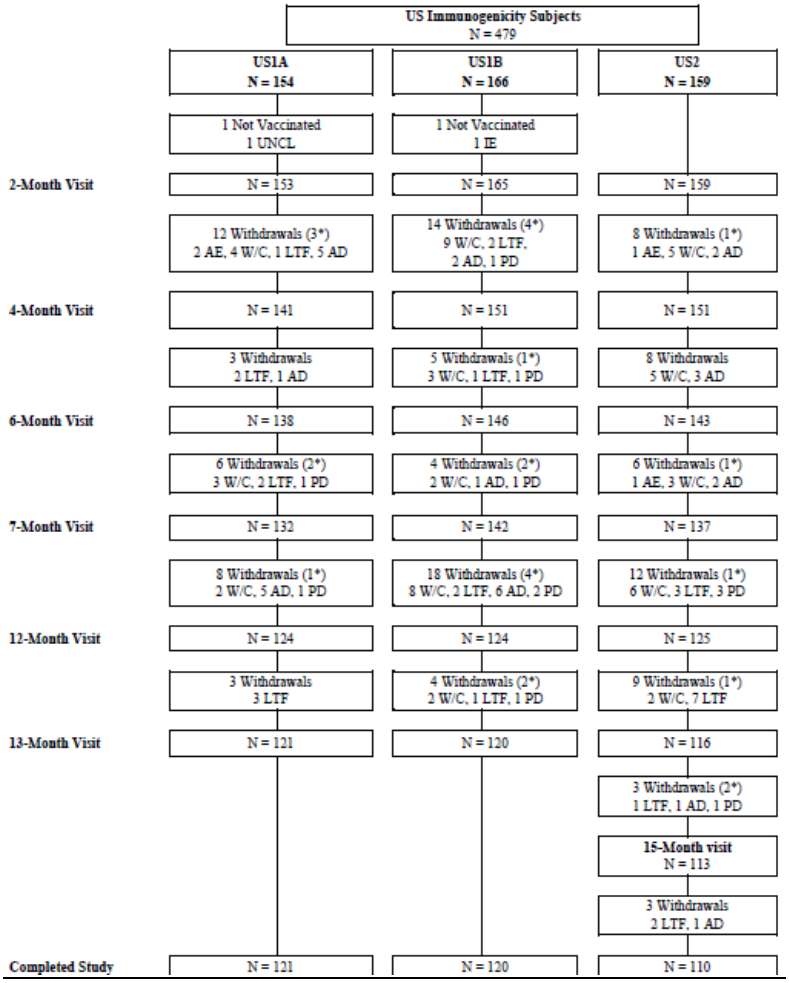
Note: 188 subjects in Group I, 190 subjects in Group II, and 175 subjects in Group III completed protocol.
Source: Table 14.1.1.1, Table 14.1.1.1.1, Table 14.1.1.2, Table 14.1.1.5, Appendix 16.2.1.1. Appendix 16.2.5.1

In study V59P22 68 subjects (23 subjects in Group I, 23 subjects in Group II and 22 subjects in Group III) enrolled at the site where GCP issues were later identified (please see 'Conduct of the study') were excluded from safety and immunogenicity analyses, and are not included in the figure above.

Study V59P14

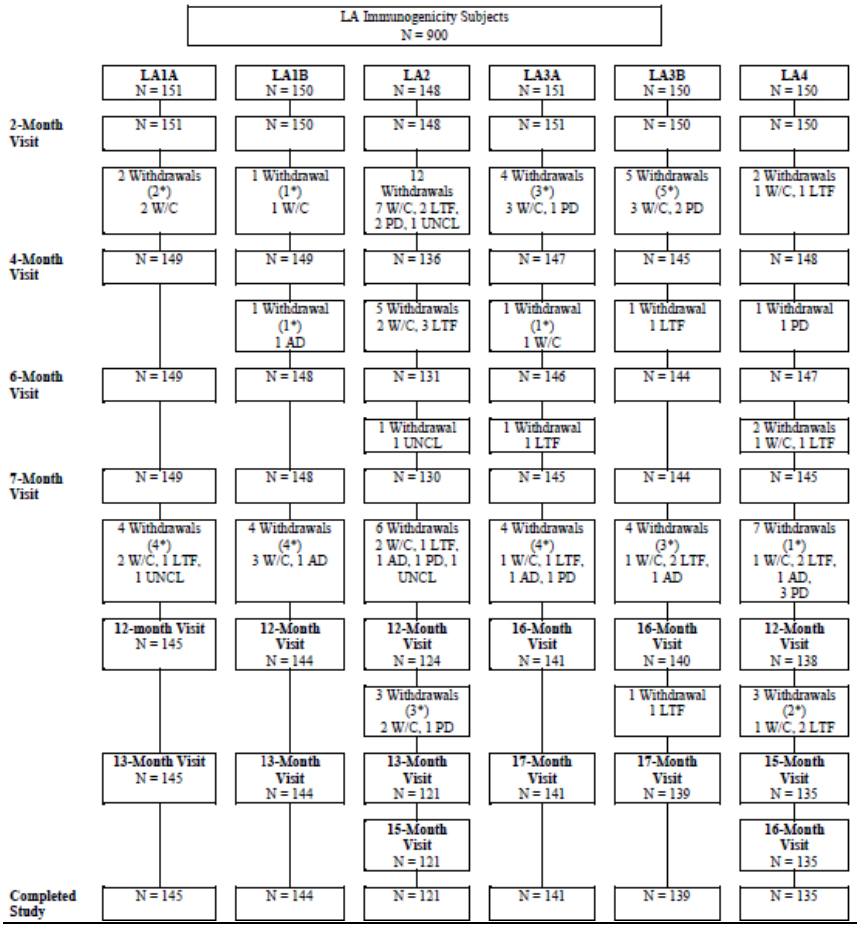
A total of 1508 subjects were enrolled in the US (479 for immunogenicity, 1029 for safety), and 3037 subjects in Latin America (Argentina and Columbia; 900 for immunogenicity (all Argentina), 2137 for safety). The disposition of subjects in the different regions is presented in the following figures for immunogenicity groups.

Figure 2. Subject Disposition Flowchart for study V59P14 –Immunogenicity Subjects in the US



* # Subjects with additional 6-month safety follow-up.
Reasons for Withdrawal: AE = Adverse Event, W/C = Withdrawal of consent, LTF = Lost to follow-up, IE = Inappropriate enrollment, PD = Protocol Deviation, AD = Administrative, UNCL = Unable to classify

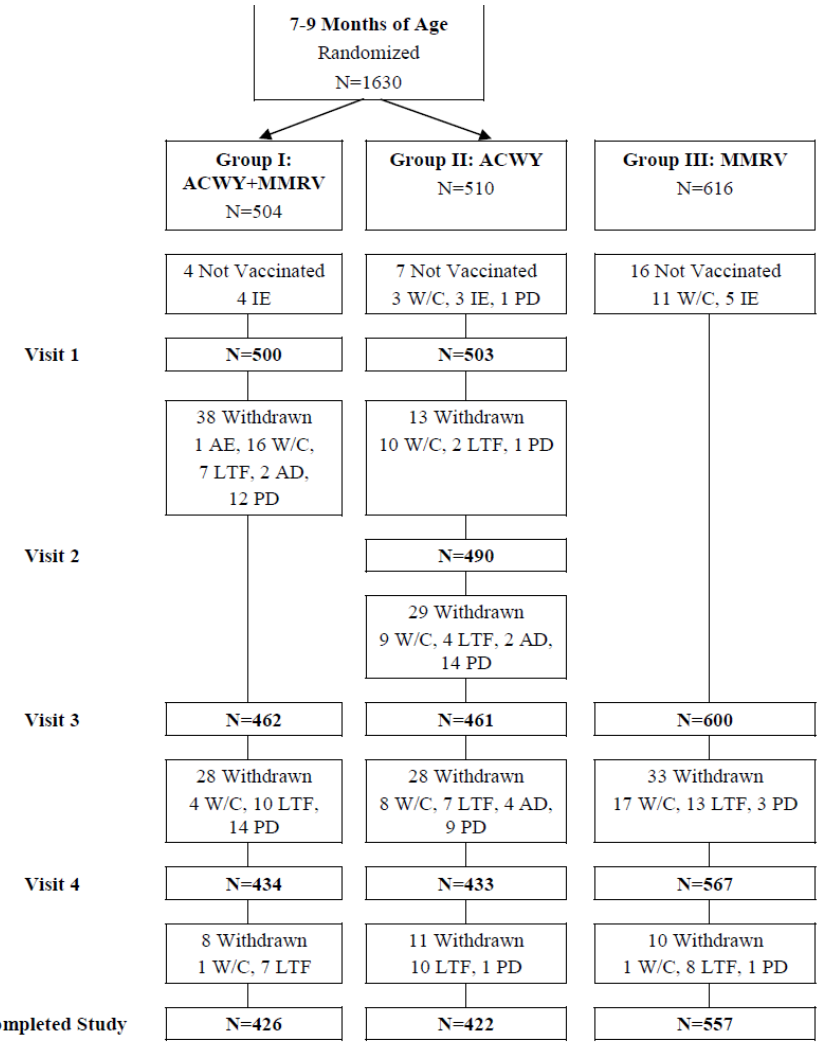
Figure 3. Subject Disposition Flowchart for study V59P14 –Immunogenicity Subjects in Latin America



Subjects with additional 6-month safety follow-up.
Reasons for Withdrawal: AE = Adverse Event, W/C = Withdrawal of consent, LTF = Lost to follow-up, IE = Inappropriate enrollment, PD = Protocol Deviation, AD = Administrative, UNCL = Unable to classify

Study V59P21

Figure 4. Subject disposition flowchart for study V59P21



Reasons for Withdrawal: AE = Adverse Event, W/C = Withdrawal of Consent, LTF = Lost to Follow-up, IE=Inappropriate Enrollment, PD=Protocol Deviation, AD=Administrative

Recruitment

Study V59P22: The first subject was enrolled on 27 March 2008; the last visit was completed on 22 October 2010.

V59P14: The first subject was enrolled on 29 March 2007; the last visit was completed on 13 November 2009.

V59P21: Date of first enrolment: 27 February 2008; date of last visit: 26 October 2010.

Conduct of the study

V59P22

In total there were 5 protocol amendments, 4 of which were after start of enrolment. Major changes included extension of the enrolment age to 6-8 months, addition of study sites in Australia, increase of

the sample size from 600 to 660, inclusion of rSBA analyses. In addition, an ad hoc analysis was performed on the primary endpoint taking into account serostatus at baseline.

Following the identification of GCP issues at one site the MAH decided to exclude all data from the affected site from the analysis and submitted a revised Clinical Study Report for study V59P22. As there were clear doubts regarding the reliability of data from this centre, the decision to not to take into account in the analysis the data from this site was supported by the CHMP. The main findings and conclusions of the trial remained unaffected, namely non-inferiority to a monovalent conjugated MenC vaccine could not be demonstrated. Findings from study V59P22 remain valid. The questioned study-site was only used for studies V59P22 and V59P22e1. The scientific discussion will include the analysis of data after removal of the data from the concerned site from both studies.

V59P14

There were 7 protocol amendments. Major amendments resulted from regulatory feedback and included the addition of a second primary endpoint (dated 03/04/2007) to assess the response to a 4 dose schedule (2, 4, 6 and 12 months), and a revision of primary endpoints (dated 27/05/2008) for all serogroups to evaluate the percentage of subjects with hSBA ≥1:8 one month post-4th dose instead of one month post-3rd dose. With the revision of the primary endpoint to support a 4 dose series, the control arms (US4 and LA6) were revised to delay the first administration of MenACWY to 13 months, providing a control group through one month after the completion of the series. In a later amendment (dated 07/08/2011) subjects in groups US4 and LA6 were to receive their 1st MenACWY at 18 months (US4C and LA6C).

In US immunogenicity subjects (US1A, US1B, US1 and US2) 52% to 65% reported major protocol deviations with US2 subjects reporting highest percentages (mostly subjects not providing a baseline blood sample). In the LA immunogenicity subjects 26% - 49% of subjects reported at least one major protocol deviation (highest in LA2). Many subjects (up to 25%) had their blood draw out of window at visit 6 which was considered to be a major protocol deviation.

V59P21

There were 5 protocol amendments, 4 after start of enrolment. The most significant changes occurred due to an interruption in ProQuad supply, which suspended study enrolment for nearly six months. The delayed study timelines resulted in extreme difficulty in completing enrolment once study enrolment resumed, allowing M-M-R II and Varivax as substitution for ProQuad administration (protocol amendments 3 and 4). Study enrolment was subsequently terminated on 18 December 2009 prior to fully enrolling 610 subjects into each group (actual numbers enrolled were 504, 510, and 616 into Groups I, II, and III, respectively). The primary change in amendment 5 (dated 04/03/2010) was addition of a main analysis to facilitate regulatory filing once the final immunogenicity data have been completed.

Enrolment at two sites was terminated prematurely:

- At one site pending implementation of appropriate corrective action plans by the Investigator to address issues of GCP compliance identified during the conduct of another Novartis Vaccines trial;
- At another site due to concerns regarding appropriate payment of subjects for study visits.

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.

Baseline data

Study V59P22

In the All Randomised Population, demographics and baseline characteristics were similar among groups.

Table 8. Demography And Other Baseline Characteristics in study V59P22 - All Randomised Population

	Group I N=219	Group II N=228	Group III N=215	Total N=662
Age (Days):	208.4±23.7	209.8±22.2	209.3±21.9	209.2±22.6
Sex:				
Male	114 (52%)	122 (54%)	121 (56%)	357 (54%)
Female	105 (48%)	106 (46%)	94 (44%)	305 (46%)
Race:				
Asian	4 (2%)	2 (<1%)	3 (1%)	9 (1%)
Black	9 (4%)	3 (1%)	3 (1%)	15 (2%)
Caucasian	200 (91%)	212 (93%)	208 (97%)	620 (94%)
Hispanic	2 (<1%)	4 (2%)	0	6 (<1%)
Other	4 (2%)	7 (3%)	1 (<1%)	12 (2%)
Met Crit.:				
Yes	198 (90%)	192 (84%)	185 (86%)	575 (87%)
No	21 (10%)	36 (16%)	30 (14%)	87 (13%)
Weight (kg):	8.07±1.11 (N=218)	8.09±0.97	8.11±0.96	8.09±1.01 (N=661)
Height (cm):	69.33±3.08 (N=218)	69.15±3.24	69.28±3.31	69.25±3.21 (N=661)

Source: Table 14.1.1.3
Categorical parameters: N (%), non-categorical parameters: Mean±Std

Study V59P14

Table 9. Demographic and Other Baseline Characteristics in study V59P14, Immunogenicity subjects in US, Randomised Population

	US1A N = 154	US1B N = 166	US1 N = 320	US2 N = 159
Age (Days):	66.1±7.2	65.8±6.6	65.9±6.9	65.7±6.5
Sex:				
Male	86 (56%)	94 (57%)	180 (56%)	88 (55%)
Female	68 (44%)	72 (43%)	140 (44%)	71 (45%)
Ethnic Origin:				
Asian	16 (10%)	14 (8%)	30 (9%)	14 (9%)
Black	26 (17%)	20 (12%)	46 (14%)	17 (11%)
Caucasian	80 (52%)	97 (58%)	177 (55%)	97 (61%)
Hispanic	20 (13%)	22 (13%)	42 (13%)	22 (14%)
Other	12 (8%)	13 (8%)	25 (8%)	9 (6%)
Weight (kg):	5.46±0.76	5.45±0.72	5.46±0.74	5.44±0.65
Height (cm):	58.52±2.60	58.66±2.45	58.59±2.52	58.21±2.31
Meet Entry Criteria:				
Yes	153 (99%)	161 (97%)	314 (98%)	157 (99%)
No	1 (< 1%)	5 (3%)	6 (2%)	2 (1%)

Table 10. Demographic and Other Baseline Characteristics in study V59P14, Immunogenicity subjects in Latin America, Randomised Population

	LA1A N = 151	LA1B N = 150	LA1 N = 301	LA2 N = 148	LA3A N = 151	LA3B N = 150	LA3 N = 301	LA4 N = 150
Age (Days):	68.0±7.7	68.6±8.9	68.3±8.3	67.8±8.3	67.0±7.9	68.4±8.7	67.7±8.3	67.5±8.0
Sex:								
Male	72 (48%)	68 (45%)	140 (47%)	76 (51%)	79 (52%)	75 (50%)	154 (51%)	69 (46%)
Female	79 (52%)	82 (55%)	161 (53%)	72 (49%)	72 (48%)	75 (50%)	147 (49%)	81 (54%)
Ethnic Origin:								
Caucasian	99 (66%)	98 (65%)	197 (65%)	98 (66%)	99 (66%)	99 (66%)	198 (66%)	99 (66%)
Hispanic	52 (34%)	52 (35%)	104 (35%)	49 (33%)	52 (34%)	51 (34%)	103 (34%)	51 (34%)
Other	0	0	0	1 (< 1%)	0	0	0	0
Weight (kg):	5.31±0.57	5.29±0.74	5.30±0.66	5.35±0.71	5.30±0.72	5.33±0.71	5.31±0.71	5.28±0.67
Height (cm):	57.02±2.90	57.31±3.08	57.17±2.99	57.37±3.17	57.09±2.70	57.47±2.87	57.28±2.79	57.16±2.87
Meet Entry Criteria:								
Yes	149 (99%)	148 (99%)	297 (99%)	146 (99%)	146 (97%)	150 (100%)	296 (98%)	148 (99%)
No	2 (1%)	2 (1%)	4 (1%)	2 (1%)	5 (3%)	0	5 (2%)	2 (1%)

Study V59P21

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.

Table 11. Demographic and other baseline characteristics in study V59P21

	ACWY + MMRV N=504	ACWY N=510	MMRV N=616	TOTAL N=1630
Age (Months):	8.5 ± 0.8	8.5 ± 0.8	12.1 ± 0.3	9.8 ± 1.9
Sex:				
Male	253 (50%)	258 (51%)	312 (51%)	823 (50%)
Female	251 (50%)	252 (49%)	304 (49%)	807 (50%)
Ethnic Origin:				
Asian	23 (5%)	22 (4%)	28 (5%)	73 (4%)
Black	68 (13%)	60 (12%)	63 (10%)	191 (12%)
Caucasian	296 (59%)	303 (59%)	384 (62%)	983 (60%)
Hispanic	65 (13%)	77 (15%)	70 (11%)	212 (13%)
Other	52 (10%)	48 (9%)	71 (12%)	171 (10%)
Weight (kg):	8.86 ± 1.19	8.87 ± 1.19	9.79 ± 1.19 (N=615)	9.22 ± 1.27 (N=1629)
Height (cm):	71.35 ± 3.90 (N=502)	71.33 ± 3.45 (N=507)	76.01 ± 3.93 (N=612)	73.10 ± 4.40 (N=1621)
Met Entry Criteria:				
Yes	472 (94%)	478 (94%)	579 (94%)	1529 (94%)
No	32 (6%)	32 (6%)	37 (6%)	101 (6%)

Numbers analysed

Study V59P22

Table 12. Overview of Study Population in study V59P22, Number (%) of Subjects

	Group I N=219	Group II N=228	Group III N=215	Total N=662
Randomized	219 (100%)	228 (100%)	215 (100%)	662 (100%)
Excluded from safety and immunogenicity (Site 18)	23 (11%)	23 (10%)	22 (10%)	68 (10%)
Safety	195 (89%)	192 (84%)	179 (83%)	566 (85%)
MITT				
MITT Post visit 1	193 (88%)	-	-	193 (29%)
MITT One month after month 12 vaccination	189 (86%)	189 (83%)	173 (80%)	551 (83%)
Per-protocol				
PP Post visit 1	182 (83%)	-	-	182 (27%)
PP One month after month 12 vaccination	168 (77%)	175 (77%)	153 (71%)	496 (75%)
PP Concomitant	168 (77%)	174 (76%)	152 (71%)	494 (75%)
PP Pertussis	161 (74%)	171 (75%)	152 (71%)	484 (73%)

Source: Table 14.1.1.1.

A total of 662 subjects were enrolled and randomized (219 in Group I, 228 in Group II and 215 in Group III). Overall, 68 subjects enrolled in site 18 (23 subjects in Group I, 23 subjects in Group II and 22 subjects in Group III) were excluded from safety and immunogenicity analyses. One subject from Group 1 withdrew consent prior to study vaccination.

Study V59P14

For the US immunogenicity groups the PP population included 323 subjects from the infant series and 267 subjects after toddler vaccination. The MITT and PP populations for the infant series differed by not more than 5% while the MITT and PP populations for toddler vaccination differed by not more than 10%. A total of 900 subjects were enrolled in the immunogenicity groups LA1, LA2, LA3 and LA4. The PP population included 825 subjects from the infant series and 629 subjects after toddler vaccination. The MITT and PP populations for the infant series differed by not more than 4% while the MITT and PP populations for toddler vaccination differed by more than 10%. The difference was mainly due to many (up to 25%) subjects having their post-toddler vaccination blood draw out of window (visit 7 blood draw for the LA4 group, and visit 6 blood draw for all other groups) which was in turn due to several amendments affecting the sampling time points.

Study V59P21

Table 13. Overview of Populations Analysed in study V59P21

	ACWY + MMRV N=504	ACWY N=510	MMRV N=616
Population:			
Randomized[a]	504 (100%)	510 (100%)	616 (100%)
Exposed	500 (99%)	503 (99%)	600 (97%)
Safety	500 (99%)	500 (98%)	597 (97%)
Safety - Follow Up	460 (91%)	453 (89%)	556 (90%)
MITT - MenACWY	455 (90%)	483 (95%)	597 (97%)
MITT - MMRV	397 (79%)	483 (95%)	536 (87%)
PP - MenACWY	389 (77%)	386 (76%)	544 (88%)
PP - MMRV	388 (77%)	402 (79%)	528 (86%)

a Only the ACWY + MMRV and ACWY groups were randomized.
PP: Per Protocol

Outcomes and estimation

Comparative Immunogenicity MenACWY vs MenC (Study V59P22)

Primary outcome

Results for the primary objective are presented in the table below.

Table 14. Proportion of subjects with serum bactericidal activity using human complement (hSBA) ≥1:8 against *N. □erogroups□s* □erogroups C at one month following one dose of MenACWY or MenC given to healthy toddlers at 12 months of age in study V59P22, PP population

	Group II (1 dose MenACWY) N=198	Group III (1 dose MenC) N=173	Group Difference
n (%)	146 (83%)	140 (92%)	-8%
95%CI	(77% - 89%)	(86% - 95%)	(-15% - -1%)

For MenACWY to be found non-inferior to MenC (Menjugate) the lower limit of the two-sided 95% CI for the difference between the percentage of subjects with hSBA ≥1:8 for serogroup C had to be greater than –10%. Results from this analysis demonstrate that the lower limit of the 95% CI group difference was not greater than -10%, therefore the primary endpoint was not met.

In order to provide a more complete understanding of the immune response to the investigational vaccine, and to provide comparative data to other studies conducted by the MAH and other sponsors, an additional secondary objective to test a subset of sera using the bactericidal assay with rabbit complement was added prior to database lock. The key immunogenicity analysis for rabbit SBA (i.e., a four-fold rise) did not achieve the non-inferiority criteria but again elicited relatively similar results for the two study groups. After MenACWY vaccination (1 dose, 140 subjects), 91% (86-95%) achieved a four-fold rise in rSBA; after MenC (1 dose, 139 subjects), 96% (92-99%) achieved a four-fold rise. The difference between the groups (-5%) had a 95% CI range of -11% to 1% and thus did not achieve non-inferiority. The rSBA GMTs were robust for both groups but higher after a single dose of MenC than after a single dose of MenACWY (266 versus 131).

Secondary outcomes

Comparative immunogenicity of 1 dose MenACWY vs. 1 dose MenC at 12 months was also assessed for GMTs and % of subjects with hSBA≥1:4.

Table 15. Geometric Mean hSBA Titers Against *N. meningitidis* Serogroup C Prior and 1 Month After 12-Month Vaccination - PP Population

	Group II (1 dose MenACWY)	**Group III (1 dose MenC)**	**GMT ratio Group II/Group III**
N GMT at visit 3 (month 12, prevaccination) 95%CI	174 **2.1** (1.8 – 2.5)	152 **2.3** (1.9-2.8)	0.92 (0.8-1.1)
N GMT at visit 4 (month 13) 95%CI	175 **22** (18-28)	153 **31** (24-39)	0.73 (0.6-0.9)
N GMR (visit 4/visit 3) 95%CI	174 **10** (8-13)	152 **13** (10-17)	0.79 (0.6– 1.0)

Following the Month 12 vaccination, the GMT increased in both vaccine groups (in Group II to 22 and in Group III to 31), with corresponding GMRs of 10 and 13, respectively. This response is consistent with typical primary immune response. The percentage of subjects with hSBA ≥1:4 towards serogroups C was 90% in Group II (95% CI: 85-94) and 97% in Group III (95% CI: 93-99).

Comparative immunogenicity of 2 doses of MenACWY (at 6-8 months and at 12 months) vs. 1 dose of MenC given at 12 months was assessed as a secondary objective.

Table 16. Percentage of Subjects with Human SBA ≥1:8 at One Month Following the 12 or 6-8 and 12-Month Vaccination, by serogroup - Primary PP Population

		Group I (2 dose MenACWY)	Group II (1 dose MenACWY)	Group III (1 dose Menjugate)	Group I - Group II	Group I - Group III	Group II - Group III
MenA-Human Complement-SBA		N=166	N=172	N=23			
	Visit 3	34 (21%) (15-29) N=159	1 (1%) (0.015-3) N=171	0 (0%) (0-15)	(21%) (15-28)	(21%) (7-28)	(1%) (-14-3)
	Visit 4	155 (93%) (88-97)	84 (49%) (41-57)	0 (0%) (0-15)	(45%) (36-53)	(93%) (79-96)	(49%) (34-56)
MenC-Human Complement-SBA		N=167	N=175	N=153			
	Visit 3	126 (78%) (71-84) N=161	6 (3%) (1-7) N=174	9 (6%) (3-11) N=152	(75%) (67-81)	(72%) (64-79)	(-2%) (-8-2)
	Visit 4	165 (99%) (96-100)	146 (83%) (77-89)	140 (92%) (86-95)	(15%) (10-22)	(7%) (3-13)	(-8%) (-15--1)
MenW-Human Complement-SBA		N=165	N=170	N=23			
	Visit 3	107 (68%) (60-75) N=157	5 (3%) (1-7) N=168	0 (0%) (0-15)	(65%) (57-72)	(68%) (53-75)	(3%) (-11-7)
	Visit 4	161 (98%) (94-99)	103 (61%) (53-68)	1 (5%) (0-23) N=22	(37%) (29-45)	(93%) (76-97)	(56%) (38-65)
MenY-Human Complement-SBA		N=163	N=167	N=23			
	Visit 3	107 (69%) (61-76) N=156	4 (3%) (1-6) N=160	0 (0%) (0-15)	(66%) (58-73)	(69%) (54-75)	(3%) (-12-6)
	Visit 4	156 (96%) (91-98)	83 (50%) (42-58)	1 (5%) (0-23) N=22	(46%) (38-54)	(91%) (74-96)	(45%) (27-54)

Source: Table 14.2.1.1.

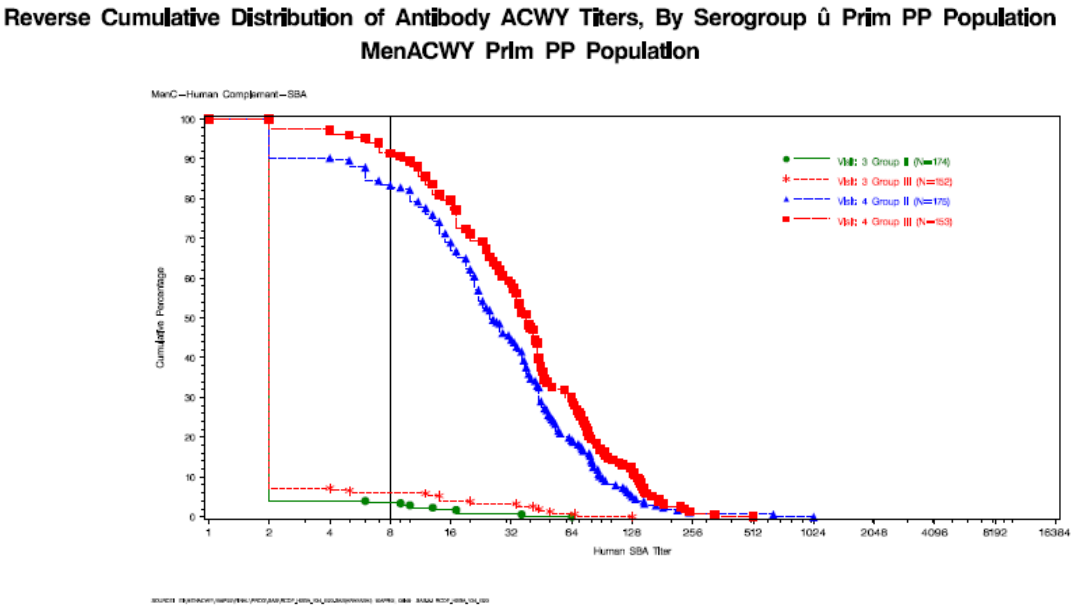
The percentage of subjects with hSBA ≥1:8 against serogroup C was 96% in Group I (2 doses of MenACWY at 6-8 and 12 months) and 86% in Group III (1 dose of Menjugate at 12 months), while the percentage of subjects with hSBA ≥1:4 against serogroup C was 97% in Group I and 91% in Group III. The hSBA GMT against serogroup C was 225 in Group I and 30 in Group III (see table below).

Table 17. Geometric Mean Human SBA Titers and Ratios at One Month Following the 12 or 6-8 and 12-Month Vaccination, by Serogroup - Primary PP Population

		Group I (2 dose MenACWY)	Group II (1 dose MenACWY)	Group III (1 dose Menjugate)	Group I : Group II	Group I : Group III	Group II : Group III
MenA-Human Complement-SBA		N=166	N=172	N=23			
	Visit 3	3.4 (2.92-3.97) N=159	1.99 (1.72-2.3) N=171	2 (1.46-2.73)	1.71 (1.47-1.99)	1.7 (1.26-2.31)	1 (0.73-1.35)
	Visit 4	75 (56-99)	10 (7.71-13)	2.22 (1.22-4.04)	7.41 (5.56-9.88)	34 (19-61)	4.55 (2.52-8.23)
	Visit 4 to Visit 3	22 (16-29) N=158	4.92 (3.75-6.46) N=168	1.11 (0.6-2.03)	4.43 (3.3-5.95)	20 (11-36)	4.45 (2.45-8.09)
MenC-Human Complement-SBA		N=167	N=175	N=153			
	Visit 3	23 (19-28) N=161	2.11 (1.77-2.51) N=174	2.29 (1.9-2.75) N=152	11 (9.21-13)	10 (8.43-13)	0.92 (0.76-1.12)
	Visit 4	249 (197-314)	22 (18-28)	31 (24-39)	11 (8.77-14)	8.1 (6.35-10)	0.73 (0.57-0.93)
	Visit 4 to Visit 3	9.85 (7.6-13) N=160	10 (8.21-13) N=174	13 (10-17) N=152	0.94 (0.73-1.23)	0.75 (0.57-0.98)	0.79 (0.61-1.03)
MenW-Human Complement-SBA		N=165	N=170	N=23			
	Visit 3	14 (11-17) N=157	2.12 (1.71-2.62) N=168	1.71 (1.06-2.74)	6.56 (5.21-8.27)	8.13 (5.11-13)	1.24 (0.78-1.98)
	Visit 4	213 (153-295)	14 (10-19)	2 (0.99-4.03) N=22	15 (11-21)	106 (53-212)	6.96 (3.48-14)
	Visit 4 to Visit 3	15 (11-21) N=155	6.64 (4.79-9.21) N=165	1.18 (0.57-2.47) N=22	2.27 (1.59-3.25)	13 (6.17-26)	5.61 (2.71-12)
MenY-Human Complement-SBA		N=163	N=167	N=23			
	Visit 3	11 (9.44-14) N=156	1.92 (1.59-2.32) N=160	1.76 (1.18-2.63)	5.96 (4.89-7.27)	6.52 (4.39-9.67)	1.09 (0.74-1.62)
	Visit 4	156 (119-205)	7.05 (5.43-9.15)	1.93 (1.06-3.52) N=22	22 (17-30)	81 (45-146)	3.64 (2.01-6.62)
	Visit 4 to Visit 3	13 (10-17) N=154	3.49 (2.7-4.51) N=155	1.06 (0.6-1.86) N=22	3.86 (2.92-5.1)	13 (7.29-22)	3.31 (1.88-5.8)

Source: Table 14.2.1.5.

Reverse Cumulative Distribution Curves



Immunogenicity of MenACWY

4 dosing schedule in infants: study V59P14

The key primary objective to support the efficacy of MenACWY in infants was that at one month after the final dose in the 4-dose series, the LL of the 2-sided 95% CI of the proportion of subjects with hSBA ≥ 1:8 was at least 80% for serogroup A and 85% for serogroups C, W and Y. This objective was tested in the US immunogenicity subjects of the pivotal study V59P14 and in the immunogenicity subjects enrolled in Latin America. For the US subjects, at 1 month after the fourth dose of MenACWY, the LL of the 2-sided 95% CI around the percentage of subjects with hSBA ≥ 1:8 was 87% for serogroup A and ranged between 92% and 96% for serogroups C, W, and Y. Similarly, 95-100% of subjects in Latin America (Group LA3A) achieved hSBA ≥ 1:8 one month after the 4th dose given at 16 months of age.

Table 18. Percentage of Subjects (95% CI) with hSBA ≥ 1:8 at 1 Month after the Proposed 4-Dose MenACWY Series (2, 4, 6, 12 or 16 Months of Age), Study V59P14 (groups US1A, LA3A)

Serogroup		US1A	LA3A
A	N % 95%CI	N =84 94% (87, 98)	N=120 95% (89, 98)
C	N % 95%CI	N=86 98% (92, 100)	N=122 98% (94, 100)
W	N % 95%CI	N=85 100% (96, 100)	N=112 100% (97, 100)
Y	N % 95%CI	N=84 100% (96, 100)	N=109 99% (95, 100)

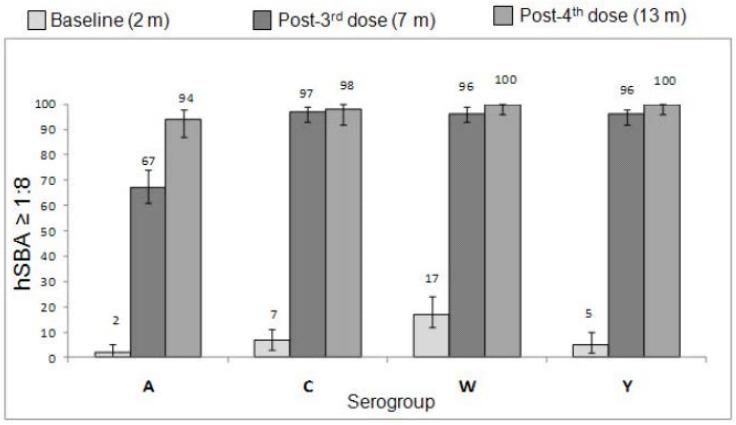
a the relevant toddler PP populations, include subjects who had at least one evaluable serogroup;
b US1A subjects are assessed at 13 months, i.e., 1 month following the fourth injection. 17 months of age for LA3A (2, 4, 6, 16 months of age vaccination schedule)

Table 19. hSBA GMTs (95% CI) at 1 Month after the Proposed 4-Dose MenACWY Series : 2, 4, 6, 12 Months of Age (US1a) vs 2, 4, 6, 16 months of age (LA3A), Pivotal Study V59P14

Serogroup		US1A	LA3A
A	N GMT 95%CI	N =84 77 (55,109)	N=120 146 (113, 118)
C	N GMT 95%CI	N=86 227 (155,332)	N=122 283 (225, 355)
W	N GMT 95%CI	N=85 416 (288,602)	N=112 727 (586, 903)
Y	N GMT 95%CI	N=84 395 (269, 580)	N=109 590 (463, 751)

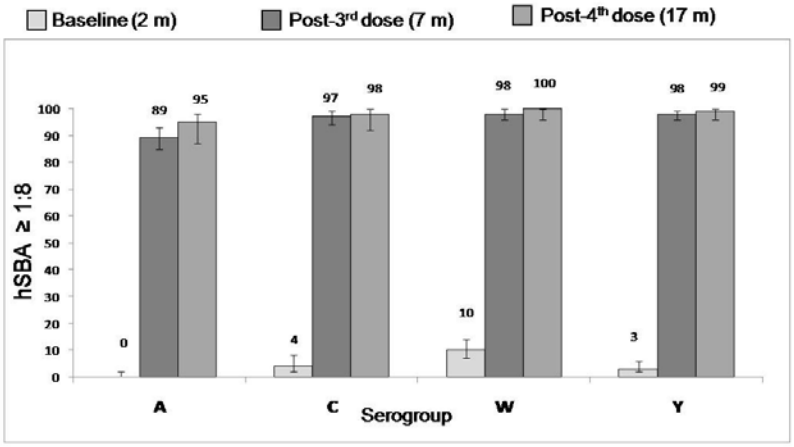
a the relevant toddler PP populations, include subjects who had at least one evaluable serogroup;
b US1A subjects are assessed at 13 months, i.e., 1 month following the fourth injection. 17 months of age for LA3A (2, 4, 6, 16 months of age vaccination schedule)

Figure 5. Percentage of Subjects (95% CI) with hSBA ≥ 1:8 at Baseline, Post-third Dose, and Post fourth Dose of a 4-dose Infant Series at 2, 4, 6, and 12 months (V59P14, US Subjects)



Note: data for group US1 for baseline and post third dose; US1A data for post fourth dose. N's for serogroup A: 2% (177), 67% (212), 94% (84), serogroup C: 7% (168), 97% (204), 98% (86), serogroup W: 17% (165), 96% (197), 100% (85), serogroup Y: 5% (150), 96% (182), 100% (84)

Figure 6. Percentage of Subjects with hSBA ≥ 1:8 at Baseline, Post-third Dose, and Post-fourth Dose of a 4-dose Infant Series (V59P14, LA Subjects)



Note: LA3 data for baseline and post third dose; LA3A data for post fourth dose. N's for serogroup A: 0 (271), 89% (268), 95% (120), serogroup C: 4% (272), 97% (272), 98% (122), serogroup W: 10% (261), 98% (264), 100% (112), serogroup Y: 3% (260), 98% (263), 99% (109)

2 dosing schedule in older infants: studies V59P14, V59P21, V59P22, V59P7

Data in support of a 2 dosing schedule in older infants (>6-12 months) comes from studies V59P21 and V59P22.

A co-primary objective of study V59P21 assessed the "adequacy" of the immune response following a 2-dose series given at 7-9 and 12 months, defined as the LL of the 2-sided 95% CI of the proportion of subjects with hSBA ≥ 1:8 was at least 65% for serogroup A and 85% for serogroups C, W, and Y at one month after the second dose. Subjects with hSBA ≥ 1:8 following the 2-dose series were 88-100%. The LL of the 2-sided 95% CI around the percentage of subjects with hSBA ≥ 1:8 was 84% for serogroup A and ranged between 93% and 98% for serogroups C, W, and Y.

Secondary objectives in study V59P22 included assessments of the immunogenicity of 2 doses of MenACWY given to infants at 6 to 8 and 12 months of age, as measured by percentages of subjects with hSBA ≥1:8 and hSBA GMTs one month after the second vaccination. It was concluded by the MAH that 2 doses were able to induce a satisfactory immune response against all 4 serotypes.

Data in support of the efficacy of MenACWY in toddlers following a 2-dose series in the second year of life mainly comes from the pivotal study V59P14 subjects in Latin America and additionally from the supportive study V59P7.

At baseline, the percentage of V59P14 Latin America subjects with hSBA ≥ 1:8 ranged between 0 and 5% across the four serogroups. After the second vaccine dose these percentages were 97% for serogroup A and 100% for serogroups C, W and Y. The LL of the 2-sided 95% CI around the percentage of subjects with hSBA ≥ 1:8 ranged between 92% and 96%.

In study V59P7, at baseline, the percentage of subjects with hSBA ≥ 1:8 ranged between 0 and 1% across the four serogroups. The immune responses observed at 1 month after the first dose of MenACWY in toddlers 12-24 months of age were modest for all four serogroups (percentage of subjects with hSBA ≥ 1:8, for serogroup A, 56%; for serogroup C, 35%; for serogroup W, 66%; for serogroup Y, 52%). Following a second dose, 6 months after the first, the proportion of subjects with an hSBA ≥ 1:8 was 86% (95% CI: 68-96) for serogroup A, and 100% (95% CI: 88-100) for serogroups C, W, and Y. Study V59P7 was not formally powered to meet the statistical criteria for 'adequacy of immune response' used in study V59P14.

1 dose schedule in older infants (at age of 12 months)

The two tables below shows, for all 4 serogroups, the results in several studies as percentages of subjects achieving hSBA ≥1:8 and as hSBA GMTs, determined from serum samples taken at one month after a single vaccination with MenACWY in toddlers 12 to 24 months of age.

Table 20. Percentage of Subjects with Human SBA ≥ 1:8 (95% CI) at One Month Following a Single Dose of MenACWY in Toddlers

Study		**V59P22**	**V59P14 (group US2)**	**V59P14 (group LA2)**	**V59P7**	**V59P8**	**V59P9**
Age at vaccination		12 m	12 m	12 m	12-24 m	12-23 m	12 m
MenA results		N=195	N=74	N=78	N=101	N=240	N=53
Pre-vaccination	n (%) 95%CI		1 (1%) (0.0034-7)	0 (0%) (0-5)			
Post-vaccination	n (%) 95%CI	49% (42-56)	53 (72%) (60-81)	58(74%) (63-84)	56% (46-66)	75% (69-81)	60% (46-74)
MenC results		N=198	N=73	N=78	N=100	N=241	N=54
Pre-vaccination	n (%) 95%CI		5(7%) (2-15)	3 (4%) (1-11)			
Post-vaccination	n (%) 95%CI	81% (75-86)	66 (90%) (81-96)	71 (91%) (82-96)	35% (26-45)	87% (82-91)	93% (82-98)
MenW135 results		N=190	N=73	N=70	N=100	N=240	N=41
Pre-vaccination	n (%) 95%CI		3 (4%) (1-12)	3(4%) (1-12)			
Post-vaccination	n (%) 95%CI	58% (51-66)	42 (58%) (45-69)	55 (79%) (67-87)	66% (56-75)	77% (71-82)	93% (80-98)
MenY results		N=188	N=68	N=71	N=99	N=238	N=54
Pre-vaccination	n (%) 95%CI		1(1%) (0.037-8)	2(3%) (0-10)			
Post-vaccination	n (%) 95%CI	49% (42,56)	38 (56%) (43-68)	51(72%) (60-82)	52% (41-62)	51% (45-58)	67% (53-79)

Source: CSR V59P14 Table 14.2.1.1.1, 14.2.1.5; CSR V59P7 Table 14.2.1.2.2; CSR V59P8 Table 14.2.1.17; CSR V59P9 Table 14.2.1.2.1, Table 14.2.1.2.3; CSR V59P22 Table 14.2.1.1

Table 21. Human SBA GMTs (95% CI) at One Month Following a Single Dose of MenACWY in Toddlers

Study		**V59P22**	**V59P14 (group US2)**	**V59P14 (group LA2)**	**V59P7**	**V59P8**	**V59P9**
Age at vaccination		12 m	12 m	12 m	12-24 m	12-23 m	12 m
MenA results		N=195	N=74	N=78	N=101	N=240	N=53
Pre-vaccination	GMT 95%CI		2.14 (1.8-2.54)	2.02 (1.7-2.4)			
Post-vaccination	GMT 95%CI	11 (8, 14)	17 (12-25)	25 (18-34)	12 (9, 16)	18 (15, 21)	11 (7.55, 16)

MenC results		N=198	N=73	N=78	N=100	N=241	N=54
Pre-vaccination	GMT 95%CI		2.26 (1.69-3.03)	2.18 (1.73-2.74)			
Post-vaccination	GMT 95%CI	23 (18, 29)	35 (23-54)	45 (34-60)	5.73 (4.4-7.48)	22 (18, 26	40 (30, 54)
MenW135 results		N=190	N=73	N=70	N=100	N=240	N=41
Pre-vaccination	GMT 95%CI		2.21 (1.69-2.9)	2.34 (1.79-3.05)			
Post-vaccination	GMT 95%CI	14 (10, 18)	11 (7.59-17)	22 (16-28)	14 (11, 19)	18 (15, 21)	30 (21, 43)
MenY results		N=188	N=68	N=71	N=99	N=238	N=50
Pre-vaccination	GMT 95%CI		2.14 (1.6-2.86)	2.2 (1.7-2.84)			
Post-vaccination	GMT 95%CI	7.5 (5.75-9.78)	10 (6.72-16)	15 (11-20)	11 (7.93, 15)	11 (8.91, 14)	10 (7.68, 14)

Source: CSR V59P14 Table 14.2.1.2.1, Table 14.2.1.16; CSR V59P22 Table 14.2.1.5; CSR V59P7 Table 14.2.1.7.2; CSR V59P8 Table 14.2.1.24; CSR V59P9 Table 14.2.1.3.1, Table 14.2.1.3.3; Note: MenACWY Toddler PP Population.

Concomitant vaccination

In Infants (study V59P14): DTaP-IPV-HBV, Hib, and Pneumococcal Conjugate vaccines

Subjects in the US1 and LA3 group received routine infant vaccinations concomitantly with three doses of MenACWY at 2, 4 and 6 months of age (infant series). Subjects in the US2 and LA4 group received the routine infant vaccinations without infant series MenACWY vaccination. In all of these groups, serum samples were collected at 7 months (one month after infant series).

One month post-infant series vaccination, the ratio of GMCs (GMCUS1 / GMCUS2) for the pertussis antigens ranged from 1 to 1.04 for the groups US1/US2, and from 0.8 to 0.93 for the groups LA3/LA4. The lower limit of two sided 95% CI was greater than 0.67 for the US subjects (US1 non-inferior to US2). The lower limit of the two-sided 95% CI was greater than 0.67 for the LA subjects (LA3 non-inferior to LA4) for PT and FHA and 0.66 for pertactin (non-inferiority not achieved). For LA subjects the ratio of GMCs (GMCLA3 / GMCLA4) or GMTs (poliovirus only) for the other antigens ranged from 0.75 to 1.07 with the lower limit of the two-sided 95% CI being greater than 0.50 (LA3 non-inferior to LA4).

In Toddlers (studies V59P22, V59P21 and V59P14): Infanrix Hexa, Prevenar, MMRV, DTaP and Hib booster

Infanrix Hexa booster (study V59P22)

The endpoint percentage of subjects with anti-diphtheria toxoid (DT) antibody concentration ≥0.10 IU/mL was 100% in all three vaccine groups. The percentage of subjects with anti-DT antibody concentration ≥1.0 IU/mL was 98-99% across vaccine groups. The percentage of subjects with antibody concentrations above ≥0.10 IU/mL against the tetanus toxoid (TT) was 100% in all three vaccine groups. The percentage of subjects with TT antibody concentration ≥1.0 IU/mL was 96-97% across the three vaccine groups. The percentage of subjects with response towards pertussis antigens (FHA, PRN, PT) was between 91% - 97% for FHA, 98-99% for PRN and 95-97% for PT. Differences between three vaccine groups were small. There were 99-100% of subjects in each of the three vaccine groups who had titres ≥1:8 against the polio antigens. There were 99% of subjects across the

three vaccine groups who had an antibody concentration 0.10 IU/mL against the Hepatitis B surface antigen. The percentages of subjects positive for Hib pre-vaccination (visit 3) were the reflection of pre-existing immunity due to prior routine vaccination with HIB containing vaccine. The percentages were much higher for the cut off level of 0.15 µg/mL that was established for the evaluation of responses after the primary series.

No obvious differences were observed between the groups in regards to immune response to Infanrix Hexa booster indicating no interference with concurrent meningococcal vaccines received at the 12 month visit.

Prevenar (study V59P22)

Immune responses against antigens of the 7 serotypes of Streptococcus pneumoniae varied among the strains, but responses were similar across the vaccine groups for the majority of the pneumococcal antigens.

MMRV (study V59P21)

The immune response to measles, mumps, rubella and varicella at six weeks following vaccination with one dose of MMRV given concomitantly with MenACWY (Group I) was to be considered non-inferior to the immunogenicity of MMRV administered alone (Group III) 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 was greater than -5% for measles, mumps and rubella and greater than -10% for varicella. The results satisfied the protocol-specified non-inferiority criterion for each of these four antigens.

This was confirmed with the immune response of MMRV as measured by GMTs for measles, mumps, rubella, and varicella for the PP population. GMTs were non-inferior in the MenACWY + MMRV group as compared to the MMRV group for all four antigens: the largest difference was observed for mumps (vaccine group ratio = 1.2, 95% CI: (1.06, 1.35)) and measles (vaccine group ratio = 1.11, 95% CI: (0.99, 1.25)) where the concomitant administration of MenACWY and MMRV had higher GMTs than the group which received MMRV alone. GMTs were consistently higher in the MenACWY + MMRV group as compared to the MMRV group for measles (4049 vs. 3632) and mumps (97 vs. 81) and were similar for rubella (57 vs. 56) and for varicella (19 vs. 18).

DtaP, Hib booster (study V59P14)

A subset of Latin American subjects of study V59P14 received the ActHib (Hib) and Infanrix (DTaP) booster vaccination at 16 months of age with (LA3A) and without (LA3B) concomitant 4th dose of MenACWY. The immune response to diphtheria, tetanus, pertussis and Hib for the group receiving concomitant MenACWY vaccination was non-inferior to that when routine vaccines were given alone except for the FHA antigen of pertussis as measured by the seroresponse rate. However, for GMC ratios non-inferiority was achieved for all antigens including FHA, for which the GMC ratio (95% CI) for LA3A vs. LA3B was: 1.14 (0.9, 1.44) i.e. above the pre-specified non-inferiority level of 0.67 for the LL of the 95% CI.

Persistence of MenACWY antibodies

Study V59P14

Persistence of bactericidal antibodies was observed for all serogroups at 12 months of age in US subjects, just prior to the fourth dose: the proportion of subjects with hSBA ≥ 1:8 for serogroups A, C,

W, and Y, respectively, was 12%, 52%, 69%, and 60%. Antibody persistence at 16 months of age prior to the fourth MenACWY dose in the subjects in Latin America, expressed as the proportion of subjects with hSBA ≥ 1:8, was for serogroups A, C, W, and Y, 15%, 26%, 63%, and 52%, respectively.

Table 22. Persistence of Antibodies as Measured by Percentage of Subjects with hSBA ≥ 1:8 and hSBA GMTs (95%CI) Prior to the 12-Month MenACWY Dose, US population, Study V59P14

Serogroup	% subjects hSBA ≥ 1:8		hSBA GMTs	
	US1[b]	US2[c]	US1[b]	US2[c]
A	N = 167	N = 74	N = 167	N = 74
	12% (7%, 18%)	1% (0.034%, 7%)	2.78 (2.48, 3.12)	2.14 (1.8, 2.54)
C	N = 169	N = 73	N = 169	N = 73
	52% (44%, 60%)	7% (2%, 15%)	8.07 (6.66, 9.77)	2.26 (1.69, 3.03)
W	N = 166	N = 73	N = 166	N = 73
	69% (62%, 76%)	4% (1%, 12%)	14 (12, 17)	2.21 (1.69, 2.9)
Y	N = 154	N = 68	N = 154	N = 68
	60% (52%, 68%)	1% (0.037%, 8%)	11 (8.98, 13)	2.14 (1.6, 2.86)

[a] the relevant toddler PP populations, i.e., N=183 (US1) and N=84 (US2), as presented in Table 3.1.3-2, include subjects who had at least one evaluable serogroup;
[b] US1 subjects are assessed at 12 months, immediately prior to the fourth MenACWY injection (US1A) or immediately prior to the administration of the 12-month routine toddler vaccines (US1B);
[c] US2 subjects are assessed at 12 months, immediately prior to receiving the first dose of MenACWY
Source: **CSR V59P14 Table 14.2.1.1.1 and Table 14.2.1.2.1.**

Table 23. Persistence of Antibodies at 16 Months of Age after 3 Infant Doses of MenACWY at 2, 4 and 6 Months - PP Population, Group LA3, Study V59P14

Serogroup	% subjects hSBA ≥1:8 (95% CI)			hSBA GMTs (95% CI)		
	Pre-1st 2 months	Post-3rd 7 months	Pre-4th 16 months	Pre-1st 2 months	Post-3rd 7 months	Pre-4th 16 months
	N=271	N=268	N=229	N=271	N=268	N=229
A	0% (0.0093, 2)	89% (85, 93)	15% (11, 20)	2.03 (1.97, 2.09)	43 (36, 52)	2.96 (2.63, 3.33)
	N=272	N=272	N=229	N=272	N=272	N=229
C	4% (2, 8)	97% (94, 99)	26% (20, 32)	2.34 (2.19, 2.49)	150 (127, 177)	4.14 (3.54, 4.84)
	N=261	N=264	N=218	N=261	N=264	N=218
W	10% (7, 14)	98% (96, 100)	63% (56, 69)	2.54 (2.31, 2.79)	182 (159, 208)	14 (12, 18)
	N=260	N=263	N=212	N=260	N=263	N=212
Y	3% (2, 6)	98% (96, 99)	52% (45, 59)	2.26 (2.14, 2.39)	125 (107, 146)	9.45 (7.81, 11)

Source: CSR V59P14 Table14.2.1.4, Table 14.2.1.5, Table 14.2.1.15, Table 14.2.2.16

Study V59P22

A secondary objective in study V59P22 was to assess the persistence of immune response against meningococcal serogroups A, C, W-135 and Y or C alone at 6-18 months after vaccination with either one or two doses MenACWY or one dose of Menjugate as measured by hSBA GMTs and percentage of subjects with hSBA ≥ 1:8 and hSBA ≥ 1:4 directed against *N meningitidis* serogroups A, C, W-135, and Y (only for subjects enrolled in Australia).

This objective was assessed in all three vaccine groups that had subjects enrolled in Australian sites, and had blood drawn at Visit 6. The actual mean time period was approximately 7 months (mean 205.5 +/- 12.9 days).

Table 24. Percentage of Subjects with Human SBA ≥1:8, ≥1:4, GMT and GMR (95% CI), at 6-18 Months Following the 12-Month Vaccination, Serogroup C Persistence PP Population

	Group I	Group II	Group III	Group I - Group II	Group I - Group III	Group II - Group III
hSBA ≥ 1:8	**N=17**	**N=14**	**N=13**			
Visit 3 (Month 12)	12 (86%) (57-98) N=14	0 (0%) (0-23)	0 (0%) (0-25)	(86%) (59-96)	(86%) (58-96)	(0%) (-23-22)
Visit 4 (Month 13)	17 (100%) (80-100)	12 (86%) (57-98)	12 (92%) (64-100)	(14%) (-6-40)	(8%) (-12-33)	(-7%) (-34-22)
Visit 6 (6-18 Months after Month 12)	12 (71%) (44-90)	9 (64%) (35-87)	7 (54%) (25-81)	(6%) (-26-38)	(17%) (-17-48)	(10%) (-25-44)
hSBA ≥ 1:4						
Visit 3 (Month 12)	13 (93%) (66-100) N=14	0 (0%) (0-23)	0 (0%) (0-25)	(93%) (67-99)	(93%) (66-99)	(0%) (-23-22)
Visit 4 (Month 13)	17 (100%) (80-100)	13 (93%) (66-100)	13 (100%) (75-100)	(7%) (-12-31)	(0%) (-18-23)	(-7%) (-31-17)
Visit 6 (6-18 Months after Month 12)	13 (76%) (50-93)	10 (71%) (42-92)	10 (77%) (46-95)	(5%) (-25-36)	(0%) (-30-31)	(-5%) (-37-28)
GMT and Ratios				**Group I : Group II**	**Group I : Group III**	**Group II : Group III**
Visit 4 (Month 13)	241 (139-419)	36 (19-66)	30 (16-56)	6.75 (2.97-15)	8.06 (3.48-19)	1.19 (0.5-2.87)
Visit 6 (6-18 Months after Month 12)	15 (7.45-29)	12 (5.65-25)	8.95 (4.15-19)	1.23 (0.45-3.35)	1.63 (0.59-4.53)	1.32 (0.46-3.85)
Visit 6 to Visit 4	0.061 (0.035-0.1)	0.33 (0.18-0.6)	0.3 (0.16-0.56)	0.18 (0.081-0.41)	0.2 (0.089-0.46)	1.11 (0.47-2.62)

The percentages of subjects maintaining bactericidal antibodies were lower than the rates found one month after the Month 12 dose (Month 13). For serogroup Y, the percentage of subjects with hSBA ≥1:8 increased in Group II from 33% responders at one month following the Month 12 dose to 79% responders at 7 months following the Month 12 dose. This trend was not seen in Group I; the percentage of responders at one month following the Month 12 dose was 100% and this decreased to 79% at the 7 month post-12 month dose time point.

Only the percentage of subjects with serogroup A bactericidal antibodies declined in Groups I and II. GMTs also declined several-fold, although the decline was less obvious in Group II for serogroups A, C and W. However, observed GMTs in Group II increased for serogroup Y. Due to small sample sizes, only limited conclusions should be drawn from these results.

Study V59P22e1 (Extension study)

This was a Phase 3, open-label, multi-centre, extension study designed to evaluate safety, tolerability, and antibody persistence at 22 to 45 months of age (13 to 33 months after last vaccination) with one or two doses of meningococcal ACWY conjugate vaccine or one dose of meningococcal C conjugate vaccine in children who participated as infants in study V59P22. A total of 205 subjects were enrolled and all subjects completed the study. At one site (site 18), several GCP findings were identified

therefore data from all subjects enrolled at this site (total 65 subjects [21 subjects in group 1, 22 subjects in group 2 and 22 subjects in group 3]) were excluded from both immunogenicity and safety analyses. Of note, the V59P22 site in Australia provided persistence data already as part of the V59P22 study (at 6-18 months after vaccination with either one or two doses MenACWY or one dose of MenC, see section above).

For the analysis subject data were clustered into periods lapsed since last vaccination: 23 months or less, 24 to 31 months, and 32 months and longer from the last vaccination. The persistence of immunity was measured as hSBA titers as a function of time elapsed since the last vaccination. A blood sample was collected before the booster dose to determine the level of bactericidal antibodies that were present. All subjects received a booster dose of MenACWY (visit 7). A blood sample to determine the booster response was collected 28 days post vaccination (visit 8).

The results of this extension study V59P22e1 demonstrate relatively modest to poor persistence of bactericidal antibodies to vaccine antigens in children 22 to 45 months of age at 13 to 33 months after previous vaccinations, consisting of one dose of MenACWY conjugate vaccine at 12 months of age (group 2), or two doses of MenACWY conjugate vaccine at 6 to 8 months and 12 months of age (group 1), or one dose of MenC conjugate vaccine at 12 months of age (group 3) in study V59P22.

Table 25. Percentage of Subjects with Human SBA ≥ 1:8 by Time Since the Last Dose of Primary Vaccination - Per Protocol Persistence Population, study V59P22e1

			Group 1	Group 2	Group 3	Group 1 - Group 2	Group 1 - Group 3	Group 2 - Group 3
≤23 months	MenA		N=25	N=17	N=19			
		Visit 7	4 (16%) (5-36)	1 (6%) (0-29)	0 (0%) (0-18)	(10%) (-13-30)	(16%) (-2-35)	(6%) (-11-27)
	MenC		N=25	N=16	N=18			
		Visit 7	9 (36%) (18-57)	6 (38%) (15-65)	8 (44%) (22-69)	(-2%) (-31-27)	(-8%) (-37-20)	(-7%) (-38-25)
	MenW		N=25	N=17	N=19			
		Visit 7	12 (48%) (28-69)	13 (76%) (50-93)	4 (21%) (6-46)	(-28%) (-53-2)	(27%) (-2-51)	(55%) (24-77)
	MenY		N=25	N=17	N=19			
		Visit 7	10 (40%) (21-61)	9 (53%) (28-77)	1 (5%) (0-26)	(-13%) (-41-17)	(35%) (11-55)	(48%) (20-70)
24-31 months	MenA		N=26	N=22	N=24			
		Visit 7	3 (12%) (2-30)	2 (9%) (1-29)	0 (0%) (0-14)	(2%) (-18-22)	(12%) (-3-29)	(9%) (-5-28)
	MenC		N=26	N=22	N=24			
		Visit 7	5 (19%) (7-39)	3 (14%) (3-35)	7 (29%) (13-51)	(6%) (-17-27)	(-10%) (-34-14)	(-16%) (-38-9)
	MenW		N=26	N=22	N=24			
		Visit 7	14 (54%) (33-73)	12 (55%) (32-76)	1 (4%) (0-21)	(-1%) (-28-27)	(50%) (27-68)	(50%) (27-70)
	MenY		N=26	N=22	N=24			
		Visit 7	10 (38%) (20-59)	6 (27%) (11-50)	7 (29%) (13-51)	(11%) (-16-36)	(9%) (-17-34)	(-2%) (-27-24)

≥ 32 months[a]	MenA		N=1	N=2	N=0	
		Visit 7	0 (0%) (0-98)	0 (0%) (0-84)		(0%) (-66-79)
	MenC		N=1	N=2	N=0	
		Visit 7	0 (0%) (0-98)	1 (50%) (1-99)		(-50%) (-91-53)
	MenW		N=1	N=2	N=0	
		Visit 7	0 (0%) (0-98)	1 (50%) (1-99)		(-50%) (-91-53)
	MenY		N=1	N=2	N=0	
		Visit 7	1 (100%) (3-100)	1 (50%) (1-99)		(50%) (-53-91)

Source: Table 14.2.1.1.1; **Bold** text indicates significance. Two vaccine groups were considered significantly different if the two-sided 95% CI for the difference in the percentage of subjects with hSBA ≥1:8 did not contain the value '0' [a]Vaccine group differences not calculated for all groups due to low numbers of subjects.

Booster response (Study V59P22e1, see description above)

One month after the booster dose of MenACWY in study V59P22e1 (visit 8), hSBA GMTs and the percentages of subjects with hSBA ≥1:8 against *N. meningitidis* serogroups A, C, W, and Y were markedly increased in both groups compared to visit 7 [serogroup A (hSBA ≥1:8 96% to 98% vs. 7% to 13%; GMT 182 to 214 vs. 2.52 to 2.82), serogroup C (hSBA ≥1:8 100% vs. 25% to 27%; GMT 541 to 968 vs. 3.91 to 3.92), serogroup W (hSBA ≥1:8 100% vs. 50% to 63%; GMT 799 to 1267 vs. 9.37 to 12), and serogroup Y (hSBA ≥1:8 100% vs. 39% to 40%; GMT 650 to 676 vs. 6.04 to 6.79)].

Induction of immunologic memory

In study V59P14, the bactericidal antibody response to a fourth dose at 12 months greatly exceeded that following a first dose at 12 months. hSBA GMTs achieved in US1A subjects were approximately 5-fold (serogroup A) to 37- and 38-fold (serogroups W and Y) higher than those observed in US2 subjects, suggesting that the three doses of MenACWY administered at 2, 4, and 6 months of age during infancy induced immunologic memory.

In study V59P9, subjects received a single dose of MenACWY at 6 months of age. The responses to the first dose at 6 months were low, with hSBA GMTs ranging between 2.96 for serogroup A to a high of 25 for serogroup C. In contrast, when these same subjects received a second dose at 12 months, the hSBA GMTs ranged from 44 for serogroup A, to 302 for serogroup C.

Study V59P16 investigated the ability to correlate levels of antigen-specific memory B-cells assessed at 5 months with antibody titres or levels of antigen-specific B- or plasma cells after vaccination with MenACWY up to 13 months of age. However, few subjects had detectable specific memory B-cells at 5 months, therefore correlations were unlikely to be reliably identified. Even though memory-specific B-cells were not easily detected at 5 months, evidence of their existence in this population was demonstrated following the 3rd vaccination by robust increases in circulating plasma cells and increased hSBA titres. Following this vaccination, ≥92% of subjects had hSBA titer ≥1:8 towards serogroups A and C, and 100% of subjects had hSBA titres ≥1:8 towards serogroups W and Y.

1.3.2.3. Supportive studies

Study V59P9

Methods

This study was designed as a phase 2, 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 enrolled: (i) healthy infants 6 months of age; and (ii) toddlers 12 months of age, which differed both in terms of vaccines received and vaccination schedules applied. Overall, a total of 175 subjects were enrolled, including 125 infants and 50 toddlers.

Infant subjects in group I (n=64) were administered MenACWY at 6 and 12 months of age, while in the other group (n=61) they received only one 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 (DTaP-IPV-Hib), and Prevenar at 6 months of age and toddler Prevnar at 12 months of age.

Relevant immunogenicity assessments/endpoints for the infant study groups were:

- immune response at 1 month after the 2-dose MenACWY series administered at 6 and 12 months of age (primary immunogenicity analysis: assessment made in terms of hSBA ≥ 1:4; secondary immunogenicity analysis: assessment made in terms of hSBA ≥ 1:8 and hSBA GMTs);
- immune response at 1 month after one dose of MenACWY administered at 12 months of age (secondary immunogenicity analysis);

Results

The immunogenicity results are presented for hSBA ≥ 1:8. At baseline, the percentage of subjects with hSBA ≥ 1:8 ranged between 0 and 4% for the four serogroups. For all four serogroups, the immune responses observed at 1 month after the 2-dose MenACWY series administered at 6 and 12 months of age were consistently higher than those observed at 1 month after a single dose of MenACWY administered at 12 months of age (percentage of subjects with hSBA ≥ 1:8, for serogroup A, 84% vs. 60%; for serogroups C and W, 100% vs. 93%, for serogroup Y, 100% vs. 67%, all respectively). This was confirmed by the results observed in the hSBA GMT analyses.

Study V59P16

Methods

Study V59P16 was designed to assess whether the frequency of meningococcal serogroup A, C, W-135 and Y specific memory B cells, measured 1 month after a 2, 4-month vaccination course with MenACWY, predicts the specific serum bactericidal activity using human complement (hSBA) of (respectively) serogroup A, C, W-135 and Y at 12 months of age (primary objective). Secondary objectives included the evaluation of the predictive value of these specific memory B cells measured at 1 month after a 2,4 month course of MenACWY for 1-2) serogroup A, C, W-135 and Y specific memory B cells and IgG concentrations and hSBA titers 1 month after a booster dose of MenACWY administered at 12 months, and at 12 months of age; 3) the rise from pre-booster levels in (respectively) serogroup A, C, W-135 and Y specific IgG, and memory B-cell concentration and hSBA titers 1 month after a booster dose of MenACWY administered at 12 months of age; and 4) the concentration of (respectively) serogroup A, C, W-135 and Y specific plasma cells and memory B-cells and specific IgG and hSBA titers in the week following a booster dose of MenACWY administered at 12 months of age.

Other secondary objectives included evaluating the possible interference with a pneumococcal conjugate vaccine, the kinetics of the appearance of serogroup A, C, W-135 and Y specific memory B cells, plasma B cells, hSBA and IgG in blood, evaluating the role of demographic factors on meningococcal serogroup A, C, W-135 and Y specific memory B cells and IgG concentrations and hSBA titers at different time points, and evaluating the effect of genetic polymorphisms on immune response to the MenACWY vaccine.

The study enrolled 216 healthy 2-month-old infants, who were assigned in a 2:1:1 ratio to one of the following vaccination groups:

- Group I – received MenACWY at 2, 4 and 12 months of age, together with a 2, 3, 4- month course of DTaP-Hib-IPV, and a 2, 4, 13-month course of PCV. MMR and a booster dose of Hib were offered at 13 months of age.
- Group II & Group III – received MenACWY at 2, 4 and 12 months of age, together with a 2, 3, 4-month course of DTaP-Hib-IPV, and a 2, 4, 12-month course of PCV. MMR and a booster dose of Hib were offered at 13 months of age. Infants enrolled in Group II had an additional blood drawn at the time of enrolment, and infants enrolled into Group III had an additional blood drawn 6-7 days following the 12 months (3rd) dose of MenACWY to assess the peak frequency of plasmablasts to the third vaccination.

For all children, a blood sample was taken 30 days following the last immunisation of the primary phase, immediately before the 3rd immunisation with MenACWY at 12 months of age and 1 month following this immunisation. A blood sample was taken from the mothers of all infants at the time of enrolment into the study.

Results

The correlation coefficients between memory B cells found at 5 months of age and hSBA titers at 12 months of age, suggested little or no correlation for serogroups A (-0.08) and C (0.31), a correlation of 0.40 for serogroup Y, and a correlation of 0.45 for serogroup W-135. The R-square indicates that for serogroups W and Y the level of titres at 12 months of age could be predicted, but for serogroups A and C the level of titres at 12 months could not be predicted. From the analysis of the primary objective it could be concluded that the prediction of hSBA titers at 12 months using only the frequency of meningococcal serogroup A, C, W-135 and Y specific memory B cells measured 1 month following a 2,4, month course of MenACWY will have large, or very large, prediction errors.

Overall, few subjects had detectable specific memory B cells at 5 months, therefore correlations were unlikely to be reliably identified. Due to the age of the infants during this study, the ability to isolate memory B cells at 5 months of age may have been limited by the small blood volumes collected (≤ 5 mL), and the fact that blood samples were divided for many immune response parameters.

However, even though memory-specific B cells were not easily detected at 5 months, evidence of their existence was demonstrated following the 3rd vaccination by robust increases in the number of circulating plasma cells and several-fold increases in hSBA titers. Following this vaccination, ≥92% of subjects had hSBA titer ≥1:8 towards serogroups A and C, and 100% of subjects had hSBA titers ≥1:8 towards serogroups W and Y.

Kinetics of the immune response suggested that following a primary vaccination with MenACWY at 2 and 4 months of age, generally, memory B cells peak approximately 7 days following vaccination and that hSBA titers peak approximately 14 days following vaccination.

1.3.2.4. Discussion on clinical efficacy

Design and conduct of clinical studies

The pivotal studies included infants from the age of 2 months. Although study V59P14 included subjects at 2 months of age, several groups in this study received their first dose of MenACWY at age 12 months.

Considering different infant vaccination schedules in the EU it is possible that MenACWY will be co-administered with conjugated pneumococcal vaccines, DtaP possibly combined with Hib, hepatitis b, and inactivated polio vaccine, measles, mumps, rubella vaccine (possibly combined with varicella vaccine), and in certain countries rotavirus vaccine and BCG[1]. All these vaccines except for BCG have been included in the clinical development program. Note that BCG is mostly given shortly after birth, and in some countries at older ages (6+ years), making concomitant administration with BCG and MenACWY unlikely, although possible. With regards to the schedules evaluated, the most strict and challenging schedule of vaccination at 2,3,4 months is not included in the assessments. Data generated with less condensed schedules cannot be extrapolated to this tighter schedule. However, as this schedule appears to be no longer used for meningococcal vaccines in the EU this forms no issue for the present variation application.

GCP issues were identified at one site from study V59P22, following which the MAH decided to exclude data from this site from the primary analysis. As such the power of the study has been reduced. However, the main findings and conclusions of the trial remain unaffected, namely non-inferiority to a monovalent MenC vaccine could not be demonstrated. Of note, the upper limit of 95% confidence interval is still negative. As the decrease in power did not change the findings from study V59P22, the CHMP concluded that study still contributes to the PIP and although the number of children included in the study is lower than what was agreed in the PIP the study findings remain valid.

In relation to study V59P22 the primary criteria for immunogenicity against serogroup C was that the lower limit of the two-sided 95% CI for the difference between one dose of MenACWY and one dose of Menjugate in the percentage of subjects with hSBA ≥1:8 at 1 month following a single vaccination at 12 months of age was greater than -10%. The (clinical) relevance of non-inferiority margins has not been discussed. A decrease in immunogenicity is expected to translate into a decrease in effectiveness and could potentially lead to a drop in the protection levels in the population possibly affecting transmission. An acceptance of lower immunogenicity of MenACWY to Menjugate should be explained in this context. A critical discussion of the difference in immune response between MenACWY and Menjugate would be essential if the MAH was to decide to apply for the indication for children aged 2-23 months.

Concerning study V59P14, the study design was drastically altered after the study was started, in order to evaluate a four dose schedule as the primary objective. In addition, a relatively large proportion of subjects in the US immunogenicity groups experienced major protocol deviations.

In this study, in both regions the baseline demographic characteristics appear well balanced between the different treatment arms. The US immunogenicity subjects appear slightly younger, heavier and longer than the LA immunogenicity subjects, however, differences are numerically small and this is not observed for the safety subjects.

[1] source: www.euvac.net

Efficacy data and additional analyses

Dose response studies

The results obtained from study V59P5 are in line with the results observed in the pivotal studies and the supportive studies: lower response and more rapid decay of bactericidal antibodies for serogroup A compared to the others, need for three doses in the primary series to infants (2,4,6 months) and good booster response at 12 months.

Comparative Immunogenicity of MenACWY vs. MenC

Regarding study V59P22, the primary objective was not met, i.e. it has not been demonstrated that MenACWY is non-inferior to Menjugate with respect to the response to serogroup C when applying a non-inferiority margin of 10%. This finding provides indication that MenACWY could be less immunogenic as compared to monovalent conjugated MenC vaccines which poses a risk concerning herd immunity against MenC. This confirms earlier observations from V59P5.

Comparative immunogenicity of 1 dose MenACWY vs 1 dose Menjugate at 12 months was also assessed for GMTs and percentage of subjects with hSBA≥1:4. The findings are in line with the primary outcome, i.e. 1 dose of MenACWY appears less immunogenic than 1 dose of Menjugate in children aged 12 months.

Comparative immunogenicity of 2 doses of MenACWY (at 6-8 months and at 12 months) vs 1 dose of Menjugate given at 12 months was assessed as a secondary objective. Clearly the immune response following 2 doses of MenACWY given at 6 -8 months and at 12 months of age is improved compared to a single dose given at 12 months, in particular when considering the GMTs. The comparison of two doses of MenACWY given at 6/8 months and 12 months vs a single dose of Menjugate given at 12 months shows a higher response after two doses of Menveo.

If Menveo is to replace monovalent conjugated MenC vaccines in childhood vaccination programs, the comparison between the vaccines for the response against serogroup C in infants is of importance. The scientific advice given in 2009 states (EMEA/CHMP/SAWP/288055/2009): “It is important to have sufficient data showing that Menveo in the group < 1 year after the primary immunizations gives an equal protection compared to the monovalent conjugated C vaccine. A small decline in the protection against type C would possibly undermine a small gain achieved by adding types A, W and Y.”

The clinical program does not include a direct comparative study versus the MenC conjugate in infants from 2 months of age. The only comparison between Menveo and conjugated MenC vaccine performed in infants is in study V59P5. One group received Menveo without adjuvant (but with polysorbate) at 2, 4 and 12 months and another group received Menjugate at the same time points. Although the number of subjects in the two groups were different, the large difference in bactericidal antibodies at all time points and the low percentage of subjects with hSBA≥1:8 at month 12 for the UK 2,4- (MenACWY) group indicates that the vaccines are not equivalent.

As non-inferiority of one dose MenACWY vs. one dose MenC in older infants / toddlers has not been demonstrated, non-inferiority can not be claimed in infants. Of note, according to the label Menjugate is given as 2 doses for infants aged 2 to 12 months with a booster dose following official recommendations and as one dose in children over 12 months of age. More doses are generally recommended for MenACWY, which is given as four doses for infants aged 2-6 months and two doses for 6-23 months (disregarding the exceptional dosing recommendation for children “at risk of exposure” between 12 and 23 months). In conclusion, there is no evidence of non-inferiority of MenACWY to a conjugated monovalent MenC vaccine in infants covered by the different MenC vaccination programmes (i.e. those who have not received a primary series of MenC vaccine).

Dosing schedules

The MAH evaluated different dosing regimens in infants: a four dose schedule in infants from 2 to 6 months of age (at 2,4,6,12-16 months), a 2 dose schedule in infants/toddlers aged 6-23 months and a one dose schedule in toddlers aged 12-23 months at risk.

Results from study V59P14 showed that the fourth dose is clearly needed to achieve sufficient immunoresponse for serogroup A in infants in US groups. The response following the 3rd dose for MenA is higher in LA subjects as compared to US subjects, but that could not be explained by higher baseline titres.

In older infants (>6-12 months), clearly 2 doses are required to amount to an adequate immune response, especially for serogroup A but also serogroups W and Y. The response post dose 1 in V59P21 for serogroups W and Y is lower than the response in study V59P22, however the response post dose 2 is similar. The observation could possibly be explained by a "ceiling effect".

In the different studies there was considerable variability in immune response to the different serogroups, for which there is no clear explanation. The MAH argued that host and environmental factors might explain some of the variability between studies.

The response after a single dose in children from 12 to 23 months is quite modest against serogroups A, W and Y – but also against C in study V59P7. It is striking that there is large variability in the response between the studies. For example, the response against serogroup W varies from 58% to 93%, and against MenC from 35% to 93%. The GMTs also show varation in response between studies, with the responses being at the higher end in study V59P9 (not for MenA and MenY). This large degree in variation is also seen between the different studies in infants after a single dose. The variation between the studies with the same presentation was equally large or possibly larger than the variation between studies with different presentations, indicating that potential differences in presentations could not explain the variability and other, currently unidentified factors play an important role.

The MAH mentions that the low response seen in the study V59P7 could be a combination of host and environmental factors rather than inherent low immunogenicity of the vaccine. In study V59P14 the effect of several cofactors, including baseline serostatus, gender, race and breastfeeding status, were evaluated however no clear relations could be found (also due to a lack of power in some cases).

Concomitant administration

In Infants (study V59P14), there is no clear evidence of interference of MenACWY with the immune response to conjugated pneumococcal vaccine, polio, hepatitis B, Hib, diphtheria and tetanus. However, response to several pneumococcal antigens is somewhat decreased when administered concomitantly with MenACWY. The clinical relevance of this observation is unclear. With regards to the response to pertussis antigens, non-inferiority of concomitant vaccination with MenACWY to vaccination without MenACWY could not be demonstrated for LA subjects for pertactin only. However, as this could be demonstrated for US subjects, and for PT/FHA, and no statistically significant difference was found considering seroresponse rates, this finding is unlikely to be important. It is agreed with the MAH that these data show that MenACWY can be administered concomitantly with routine infant vaccines without impact on the response to the concomitant vaccine antigens.

In toddlers (studies V59P21, V59P14), there was no evidence of interference of MenACWY with MMR-V, Hib booster and Tdap in toddlers. It is agreed with the MAH that MenACWY can be administered concomitantly with routine toddlres vaccines without impact on the response to the concomitant vaccines antigens.

Persistence data

Persistence data has been presented for up to 5 months after completion of 3 doses in the primary series (2,4,6 months) in infants and up to 7 months after a two-dose schedule in older infants and toddlers (very limited number of subjects). The weak point is the serogroup A component where a very rapid drop in bactericidal antibodies was observed. In the US part of study V59P14 (Group US1) only 12% of subjects had hSBA≥1:8 against serogroup A before the fourth dose at 12 months, compared to 52% for serogroup C, 69% for serogroup W and 60% for serogroup Y. The drop for serogroup A was from 67% 1 month after the third dose to 12% just before the fourth dose. In the Latin-America (LA) part of study V59P14 the fourth dose was given at month 16 which means that persistence was observed for up to 9 months after the sampling at month 7 (after dosing at 2,4,6 months). Again, serogroup A was down to 15% with hSBA≥1:8, serogroup C down to 26%, serogroup W 63% and serogroup Y 52%. This means there is a risk that in a time window after the third dose a majority of subjects are below the protective level of bactericidal antibodies. A period of 10 months between the third and fourth dose is considered too long to ensure that most subjects are protected.

A secondary objective in study V59P22 was to assess the persistence of immune response against meningococcal serogroups A, C, W-135 and Y or C alone at 6-18 months after vaccination with either one or two doses MenACWY or one dose of Menjugate as measured by hSBA GMTs and percentage of subjects with hSBA ≥ 1:8 and hSBA ≥ 1:4 directed against *N meningitidis* serogroups A, C, W-135, and Y (only for subjects enrolled in Australia). It is agreed with the MAH that due to small sample sizes limited conclusions can be drawn from this data. Serogroup A dropped to 31% with hSBA≥1:8 in group I (2 doses MenACWY at 6-8 months and 12 months) and to 7% in group II (1 dose MenACWY at 12 months), confirming observations from other studies that the persistence of bactericidal antibodies against serogroup A is weak.

The results of an extension study of V59P22 demonstrated limited persistence of bactericidal antibodies at 22 to 45 months of age (13 to 33 months after the primary vaccinations). Percent of subjects with hSBA.1:8 directed against serogroups C, W, and Y were higher than those for serogroup A in the respective all study groups. These results show 14% to 55% of subjects having hSBA≥1:8 at 24 to 31 months after one or two doses of MenACWY for serogroups C, W and Y.

In study V59P22e1 robust hSBA responses to booster vaccination with MenACWY were demonstrated for all groups 13 to 33 months after the primary vaccination. In addition, the study demonstrated that MenACWY can effectively boost the response to serogroup C in subjects primed with MenC conjugate (group 3), which was comparable to the booster response in groups primed with MenACWY (groups 1 and 2).

During the MAA rapid waning of bactericidal antibodies, especially for serogroup A was considered of major concern. Moreover, in the initial Scientific Advice based on the data from study V59P5 it was noted that the SBA response rates in the MenACWY groups (both adjuvanted and non-adjuvanted formulations) were significantly lower when compared to Menjugate at 12 months of age. In this study, the persistence of Menjugate (given at 2 & 4 months) was better, with 90% hSBA ≥1:4 at 12 months compared to 30-73% for the different MenACWY groups. This was considered of great concern and it was requested that this was to be addressed in the infant program. The MAH has failed to do so adequately: The present data from groups US1 and group LA3 again points towards modest persistence at 12 or 16 months of age following 3 doses given at 2, 4 and 6 months, depending on the serogroup (ranging from 12/15% for MenA to 63/69% for MenW). The limited comparison for persistence of bactericidal antibodies with licensed MenC vaccines in this age group point towards similar persistence for serogroup C compared to Menjugate, however this comparison is made upon only very few subjects in each arm (17, 14, 13) which is too little to make firm conclusions. Extrapolations of data from older subjects cannot be made, as the immune system of an infant and

toddler cannot be compared to that of an adolescent or of adults. Study V59P14e1, which is ongoing, shall provide persistence data up to 60 months; however these data are currently not available.

Immunologic memory

It has become increasingly clear that for diseases with rapid clinical progression, such as meningococcal disease, sustained bactericidal antibodies are important for individual protection. Ability to induce T-cell-dependent immunity is a fundamental property that defines a conjugate vaccine, and evidence showing that MenACWY can induce immunologic memory is important, as it has broader implications for characterizing the vaccine.

The results of studies V59P14, V59P9 and V59P16 (please see section 'Induction of immunologic memory') demonstrate that immunologic memory was induced in young infants when exposed to MenACWY in the first year of life not only after exposure to three MenACWY doses, but also after a single MenACWY dose.

Although persistence of bactericidal antibodies is recognised as the key determinant of long term protection against meningococcal disease due to the fact that disease has such fast onset that anamnestic immune response is sometimes too late to protect the individual, the demonstration of the ability of MenACWY to induce immunologic memory is also important, contributing to the overall confidence that MenACWY possesses the broad characteristics of a glycoconjugate vaccine. In an ongoing extension study of V59P14, study V59P14E1, it is planned to evaluate persistence of bactericidal antibodies to 40 and 60 months of age with an assessment of immunologic memory at 60 months of age.

The discussed studies provide some evidence of the induction of immunologic memory therefore exhibiting the characteristics of a glycoconjugate vaccine. However, it is more relevant to have good persistence of bactericidal antibodies.

Supportive studies

Study V59P9 clearly supports a 2 dose schedule over a 1 dose schedule in infants aged over 6 months.

Data from study V59P16 indicated that subjects could be protected 14 days after vaccination, which could direct a recommendation for travellers (i.e. the optimal immune response in infants is achieved around 14 days following vaccination), however this cannot be extrapolated to adults and older children.

1.3.2.5. Conclusions on the clinical efficacy

The MAH submitted three large phase III trials (V59P14, V59P21 and V59P22) and several phase II studies in support of this variation application, initially submitted to extend the indication for MenACWY to include children aged 2 to 23 month. The data point out that MenACWY elicits an immune response in infants and toddlers. Four doses at 2, 4, 6 and 12-16 months resulted in a seroresponse (% with hSBA ≥ 1:8, 95%CI) at one month after the last dose of 94% (87,98), 98% (92,100), 100% (96,100) and 100% (96,100) for serogroup A, C, W and Y respectively. One month following a two dose schedule in infants aged 6 to 9 months (with the second dose given at 12 months) 88-90%, 96-100%, 96-100%, 92-96% of subjects achieved hSBA ≥1:8 for serogroups A, C, W and Y respectively. One month following one dose in children from 12-23 months of age, 49-75%, 35-93%, 58-93%, and 49-72% of subjects achieved hSBA ≥1:8 for serogroups A, C, W and Y respectively across the different subjects.

There is no evidence of non-inferiority of MenACWY to a conjugated monovalent MenC vaccine in infants and toddlers covered by the different MenC vaccination programmes (i.e. those who have not received a primary series of MenC vaccine), which has implications for the use of this vaccine in the EU setting.

A one dose schedule as previously proposed for children "at risk of exposure" from 12 – 23 months is not supported by the data.

There is paucity in comparative persistence data with a monovalent conjugate MenC vaccine demonstrating equal persistence for MenC and no long term persistence data for all serogroups (12 months at the minimum). Moreover, persistence for serogroup A is poor. A warning concerning this has been included in the SmPC following variation II/17.

Furthermore, the data indicate that there is a period between the third and fourth dose when a substantial proportion of subjects have no protective levels of bactericidal antibodies. A period of 6 to 10 months between the third and fourth dose in the infant schedule, as is currently recommended, is thus considered too long to ensure sufficient levels of protection.

The above mentioned issues remain unsolved and therefore valid, if the new indication was still requested. During the procedure the MAH applied for a change in the scope of the variation, requesting only update of the SmPC with results from studies conducted in line with the agreed PIP.

1.3.3. Clinical safety

1.3.3.1. Introduction

This section mainly presents and discusses the safety data presented for the age group of 2 – 23 months.

1.3.3.2. Patient exposure

Table 26. Patient exposure (2 – 23 months), all studies in infants, all formulations

Study ID	Test Products, Dosage Regimen, Route of Administration	Subjects by arm	Age groups included
V59P2	• MenACWY 10-10-10-10µg Ad+ IM • MenACWY 0-10-10-10 µg Ad+ IM • MenACWY 10-5-5-5 µg Ad+ IM • MenACWY 5-5-5-5 µg Ad+ IM • MenACWY 2.5-2.5-2.5-2.5µg Ad+ IM • Menjugate® IM	• 109 • 106 • 103 • 101 • 104 • 97	Toddlers (12-16 months)
V59P4	• MenACWY10-10-10-10µg Ad- IM • MenACWY5-5-5-5µg Ad-IM • MenACWY5-5-5-5 µg Ad+ IM • Menomune® SC	• 81 • 79 • 75 • 80	Toddlers (12-16 months): MenACWY Children (3-5 years): Menomune®
V59P5	• MenACWY+ & MenACWY+ Boost IM • MenACWY+ & no Boost IM • MenACWY+ followed by 1/5th Dose Menomune® SC • MenACWY- & 10-5-5-5 µg Ad- Boost IM • MenACWY- followed by 1/5th Dose Menomune® SC	• 229 • 49 • 98 • 135 • 45	Infants (2 months)

	• Menjugate® & MenACWY+ Boost IM	• 45	
V59P7	• MenACWY10-5-5-5 µg Ad+ IM • MenACWY10-5-5-5 µg Ad– IM • Mencevax® IM followed by MenACWY10-5-5-5 µg Ad–IM	• 205 • 331 • 81	Toddlers (12-35 months) Children (36-59 months)
V59P8	• MenACWY • MenACWY (+PnC) • MenACWY (+ DTaP) • Menomune® SC	• 453 • 71 • 73 • 310	Children (2-10 years) Toddlers (12-23 months)
V59P9	• MenACWY • Menjugate® followed by MenACWY	• 125 • 50	Infants (6 -12 months)
V59P16 Non-IND Study	• MenACWY	• 216	Infants (2 months)
V59P14	• MenACWY (+ Routine Vaccines) • Routine Vaccines Only Followed by MenACWY	• 3022 • 1511	Infants (2 months)
V59P21	• MenACWY followed by MenACWY plus ProQuad® SC • MenACWY followed by MenACWY IM followed by ProQuad® • ProQuad® SC	• 500 • 503 • 600	Infants (7-9 months)
V59P22	• MenACWY 2x • MenACWY • Menjugate® IM	• 196 • 205 • 193	Infants (6 months)
V59P23	• MenACWY + routine vaccines • Routine vaccines only	• 2843 • 997	Infants (2 months)

Table 27. Safety Populations included in the Summary of Clinical Safety, Infants, older infants & toddlers.

	MenACWY[a]				**MenC**	**Control [b]**	
Study	**4-dose series [c]**	**3-dose series [c]**	**2-dose series**	**1-dose series**		**3 doses (through 12 months of age)**	**4-dose control**
V59P5	0	135	0	0	0	0	0
V59P8	0	0	0	289	0	0	0
V59P9	0	0	64	56	50	0	0
V59P14	2720	301	921	0	0	1511	626
V59P16	0	216	0	0	0	0	0
V59P21	0	0	1000	0	0	0	0
V59P22[d]	0	0	195	192	179	0	0
V59P23	2843	0	0	0	0	997	997
Total	**5563**	**652**	**2180**	**537**	**229**	**2508**	**1623**

a All subjects received routine vaccinations concomitantly with MenACWY. See protocols for details of type of concomitant vaccine at different injection timepoints.

b Control subjects: 2, 4, 6 controls for infant dosing. 4-dose controls are the subset of control subjects who did not receive MenACWY until after the 4th study vaccination (Study V59P14: Groups US4b, US4c, LA6b, LA6c) or who never received MenACWY (V59P23)'.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 months of age dose was given concomitantly with ProQuad, Prevnar, and Havrix and the 15 months of age dose was given concomitantly with Infanrix and ActHIB.
c V59P14: 4-dose series given at 2-4-6-12 (US 1a, US3, LA5), 2-4-6-13 (US1b), 2-4-6-16 (LA3a), or 2-4-6-17 (LA3b) months of age. V59P23: 4-dose series given at 2-4-6-12 months of age. V59P14: 3-dose series given at 2-6-12 (LA1a) or 2-6-13 (LA1b) months of age. V59P5 and V59P16: 3-dose series given at 2-4-12 months of age.
[d] respectively 23, 23 and 22 subjects were removed from the 2-dose, 1-dose and MenC groups following the removal of site 18 from study V59P22
Source: Integrated Safety Summary – EMA Response Table 1&2

1.3.3.3. Adverse events

Solicited Adverse Events

Reactogenicity

For the infant subjects, the percentages of subjects who experienced local or systemic reactions after any vaccination were very similar between the 4-dose MenACWY series and 4-dose control groups. The percentage of older infant/toddler subjects reporting any severe reactogenicity appears lower after 2-dose (12%) or 1-dose (16%) MenACWY compared to MenC (27%) (any vaccination). In this age group there was no difference in local reactogenicity between the three groups (51%, 50%, 51%, respectively). There was a higher percentage reporting systemic reactions in the MenC group (80% any, 25% severe) in comparison to the 2-dose (64% any, 11% severe) and 1-dose (72% any, 14% severe) MenACWY groups.

The percentages of infants, older infants and toddlers who experienced any local or systemic reaction following each vaccination are presented in the tables below.

Table 28. Percentage of Subjects Reporting Any (and Severe) Local and/or Systemic Reactions, After Each Vaccination – Infants (V59P5, V59P14, V59P16, V59P23)

	2-mo ACWY (N=4618)	**2-mo Control (N=1931)**	**4-mo ACWY (N=4161)**	**4-mo Control (N=1695)**	**6-mo ACWY (N=3916)**	**6-mo Control (N=1756)**	**Toddler ACWY (N=4032)**	**Toddler Control (N=942)**
Any reaction								
Any	4142 (90%)	1730 (90%)	3451 (83%)	1404 (83%)	2840 (63%)	1310 (75%)	2751 (68%)	663 (70%)
Severe	412 (10%) (N=4267)	237 (12%)	221 (6%) (N=3810)	142 (8%)	165 (4%)	86 (5%)	197 (5%) (N=3703)	47 (5%)
Local reaction								
Any	2950 (64%)	1297 (66%)	2386 (57%)	1053 (62%)	1799 (46%)	934 (53%)	1782 (44%)	447 (47%)
Moderate + Severe	219 (5%) (N=4267)	164 (8%)	102 (3%) (N=3810)	78 (5%)	45 (1%)	38 (2%)	48 (1%) (N=3703)	14 (1%)
Systemic reaction								
Any	3501 (76%)	1422 (74%)	2645 (64%)	1076 (63%)	2005 (51%)	901 (51%)	1942 (48%)	475 (50%)
Severe	252 (6%) (N=4267)	109 (6%)	154 (4%) (N=3810)	83 (5%)	128 (3%)	53 (3%)	161 (4%) (N=3703)	35 (4%)

Analgesic Use								
Any	2922 (63%)	1254 (65%)	2396 (58%)	1004 (59%)	1833 (47%)	876 (50%)	1499 (37%)	379 (40%)

Note: excludes subjects from one site in V59P14 and V59P23.
Local and Systemic reactions were: tenderness, erythema, induration, change in eating, sleepiness, persistent crying, irritability, vomiting, diarrhea, fever, rash (not collected in V59P5). Moderate+Severe induration/erythema: > 50 mm; severe fever: ≥ 39.0oC. Rash not included in severe systemic summary because severity is not assessed. For local reactogenicity assessment in the control group, ActHIB and Prevnar were the reference vaccines for the infant series and toddler vaccination, respectively for study V59P14. For study V59P23, Prevnar was the reference vaccine for all visits. No local reactogenicity reference vaccine was included for study V59P5.

Table 29. Percentage of subjects reporting any (and severe) local and/or systemic reactions, after each vaccination

		Dose 1 (N = 2667)	**Dose 2 (N = 1991)**	**MenC (N = 229)**
Any reaction	Any	1909 (72%)	1253 (61%)	205 (90%)
	Severe	205 (8%) (N=2547)	139 (7%) (N=1932)	48 (27%) (N=179)
Local	Any	1095 (41%)	725 (36%)	121 (53%)
	Moderate + Severe	33 (1%) (N=2547)	32 (2%) (N=1932)	9 (5%) (N=179)
Systemic	Any	1470 (55%)	889 (45%)	184 (74%)
	Severe	189 (7%) (N=2547)	112 (6%) (N=1932)	45 (25%) (N=179)
Analgesic Use	Any	865 (32%)	477 (24%)	78 (34%)

Note: excludes subjects from one site in V59P14 and V59P21 and site 18 in V59P22.
Local and Systemic reactions were: tenderness, erythema, induration, change in eating, sleepiness, persistent crying (not collected in V59P9), irritability, vomiting, diarrhea, fever, rash (not collected in V59P8, V59P9). Moderate+Severe induration/erythema: > 50 mm; severe fever: ≥ 39.0oC. Rash not included in summary because severity is not assessed.

For infants, the percentages of subjects who experienced reactions were very similar between the MenACWY and control groups after vaccinations at 2 months, 4 months, and 6 months of age, and in the toddler year. The greatest difference (7%) was found in the percentage of subjects experiencing any local reactions in the 6-month MenACWY group (46%) and 6-month control group (53%). Also, the percentages decreased after each vaccination in both the MenACWY and control groups. The percentages of older infant/toddler subjects who experienced any local or systemic reactions were higher following the first dose (72%) than after the second dose (62%). This was also true for local reactions (41% and 36% following dose 1 and dose 2, respectively), systemic reactions (55% and 45%), and analgesic use (32% and 24%). In the integrated analysis, subjects who received a single vaccination with MenC experienced more reactions (90%), more local (53%), and more systemic reactions (80%) than those that received MenACWY, and they also experienced more severe reactions (27%), more moderate+severe local reactions (5%), and more severe systemic reactions (25%).

Local Reactogenicity

In general, the percentages of infant subjects who experienced particular local reactions (tenderness, erythema, and induration) 1 to 7 days after *any vaccination* were somewhat lower in the 4-dose MenACWY group than in the 4-dose control group. A similar picture is seen when considering local

reactions after *each vaccination* in this age group. The percentages of older infants/toddlers who experienced particular local reactions (tenderness, erythema, and induration) 1 to 7 days after any vaccination were similar between the 2-dose and 1-dose MenACWY groups. Those that received MenC experienced less tenderness, about the same erythema, and more induration than the MenACWY subjects.

The percentages of older infants/toddlers who experienced any tenderness 1 to 7 days after each vaccination were similar between the MenACWY dose 1 group (23%), MenACWY dose 2 group (22%), and the MenC group (25%), though severe tenderness was higher in the MenC group (4%) than both MenACWY groups (1% in both). A higher percentage of subjects experienced erythema in the MenC group (38%) than in the MenACWY dose 1 and dose 2 groups (27% and 24%, respectively). Severe erythema was ≤ 1% in all groups. A higher percentage of subjects experienced induration in the MenC group (26%) than in the MenACWY dose 1 (13%) and dose 2 groups (10%).

Systemic Reactogenicity

Overall, the percentages of infant subjects who experienced particular systemic reactions after *any vaccination* were very similar between the 4-dose series and 4-dose control groups. The most commonly reported systemic reaction was irritability (69% and 72% in the 4-dose MenACWY and 4-dose control groups, respectively), followed by sleepiness (66% and 67%), and persistent crying (55% and 58%). The percentages of severe reactions were low, never exceeding 5% for any solicited reaction in the MenACWY vaccine group, and 5% in the control group. Fever was experienced by similar percentages across groups (range: 24-26%); fever ≥ 40°C occurred in < 1% of subjects in both groups across vaccinations. Most reactions occurred within 1-3 days after vaccination.

During the 7-day reporting period following any vaccination, in the 2-dose MenACWY group, the most commonly reported systemic reactions after any vaccination were irritability (45%), sleepiness (33%), and persistent crying (25%) in older infant/toddler subjects. In the 1-dose MenACWY group, the most commonly reported systemic reactions were irritability (44%), sleepiness (41%), and change in eating habits (26%). In the MenC group, the most commonly reported systemic reactions after any vaccination were irritability (45%), sleepiness (46%), and persistent crying (43%). Fever occurred in 41% of MenC subjects compared to 23% and 17% in the MenACWY dose 1 and dose 2 subjects. Fever ≥ 40°C was experienced by ≤ 1% of subjects in all groups. This discrepancy may be due to the fact that a majority of the MenC subjects were in study V59P22 which measured temperature rectally as opposed to the axillary method used in all other studies. In that study the comparison of fever ≥ 38°C after one dose of MenACWY and MenC at 12 months of age was unremarkable: 29% versus 25% for MenACWY and MenC, respectively. Most reactions occurred within 1-3 days after vaccination.

The percentages of older infant/toddler subjects reporting systemic reactions, 1-7 days after each vaccination are presented by severity in the table below.

Table 30. Percentages of Subjects Reporting Any Systemic Reactions by Severity, 1-7 Days after Each Vaccination – Older Infant/Toddlers (studies V59P8, V59P9, V59P14, V59P21, V59P22)

		MenC Dose 1	**MenACWY Dose 1**	**MenACWY Dose 2**
		(N = 229)	(N = 2667)	(N = 1991)
Change in Eating Habits	**N**	**226**	**2610**	**1902**
Any		63 (28%)	443 (17%)	237 (12%)
Present*		14 (6%)	31 (1%)	13 (1%)
Mild		24 (11%)	275 (11%)	149 (8%)
Moderate		19 (8%)	110 (4%)	60 (3%)

Severe		6 (3%)	27 (1%)	15 (1%)
Persistent Crying	**N**	**176**	**2491**	**1842**
Any		76 (43%)	439 (18%)	264 (14%)
Present*		0	0	0
Mild		31 (18%)	275 (11%)	169 (9%)
Moderate		28 (16%)	125 (5%)	74 (4%)
Severe		17 (10%)	39 (2%)	21 (1%)
Sleepiness	**N**	**229**	**2663**	**1990**
Any		106 (46%)	725 (27%)	389 (20%)
Present*		12 (5%)	47 (2%)	20 (1%)
Mild		43 (19%)	457 (17%)	262 (13%)
Moderate		30 (13%)	172 (6%)	81 (4%)
Severe		21 (9%)	49 (2%)	26 (1%)
Irritability	**N**	**229**	**2664**	**19990**
Any		102 (45%)	932 (35%)	566 (28%)
Present*		29 (13%)	76 (3%)	34 (2%)
Mild		38 (17%)	600 (23%)	382 (19%)
Moderate		24 (10%)	204 (8%)	118 (6%)
Severe		11 (5%)	52 (2%)	32 (2%)
Vomiting	**N**	**229**	**2663**	**1990**
Any		20 (9%)	195 (7%)	87 (4%)
Present*		4 (2%)	12 (< 1%)	3 (< 1%)
Mild		7 (3%)	145 (5%)	66 (3%)
Moderate		7 (3%)	26 (1%)	13 (1%)
Severe		2 (1%)	12 (< 1%)	5 (< 1%)
Diarrhea	**N**	**229**	**2663**	**1990**
Any		49 (21%)	355 (13%)	178 (9%)
Present*		7 (3%)	17 (1%)	8 (< 1%)
Mild		22 (10%)	242 (9%)	116 (6%)
Moderate		12 (5%)	72 (3%)	42 (2%)
Severe		8 (3%)	24 (1%)	12 (1%)
Rash	**N**	**179**	**2254**	**1931**
Any		7 (4%)	107 (5%)	73 (4%)
Other		3 (2%)	55 (2%)	44 (2%)
Urticarial		4 (2%)	52 (2%)	29 (2%)
Fever (≥ 38oC)	**N**	**229**	**2660**	**1984**
Yes		95 (41%)	311 (11%)	206 (10%)
Analgesic use	**N**	**229**	**2660**	**1989**
Yes		78 (34%)	864 (32%)	477 (23%)
Temperature (°C)	**N**	**229**	**2660**	**1984**
Any		95 (41%)	310 (12%)	206 (10%)
38.0 - < 38.5 C		46 (20%)	125 (5%)	92 (5%)
38.5 - < 39.0 C		29 (13%)	101 (4%)	67 (3%)

39.0 - < 39.5 C		15 (7%)	57 (2%)	29 (1%)
39.5 - < 40.0 C		4 (2%)	16 (1%)	13 (1%)
≥ 40 C		1 (< 1%)	11 (< 1%)	5 (< 1%)

Note: excludes subjects from one site in V59P14 and V59P21 and site 18 in V59P22

Unsolicited Adverse Events

For the infant series (2 to 7 months of age), 68% and 67% of subjects experienced treatment-emergent AEs in the MenACWY and control groups, respectively. The most common AEs during this period were upper respiratory tract infections (20% and 18% in MenACWY and control groups, respectively), otitis media (12% and 11%), nasopharyngitis (6% and 8%), and bronchiolitis (7% and 8%). Twenty eight (28) percent of older infants/toddler subjects experienced any AE following 1 dose of MenACWY. The most common AEs for this one month time period were otitis media (4%), teething (3%), and upper respiratory infection (3%). In the MenC group 43% of subjects experienced any AE in the one month following vaccination. The most common AEs in this group were pyrexia (6%) and induration (5%).

A summary of all possibly or probably related treatment-emergent AEs and possibly or probably related severe AEs for infant subjects who received MenACWY is presented in the table below.

Table 31. Summary of Possibly or Probably Related (and Possibly or Probably Related Severe) Treatment-Emergent AEs during Infant Series Vaccination (Preferred Terms Occurring in ≥ 1% of Subjects), MenACWY Subjects, by Time Period

	Infant series		**1 month after first toddler dose**	
	ACWY		ACWY	
	(N = 6215)		(N = 5445)	
	Poss/prob related	Poss/prob related severe	Poss/prob related	Poss/prob related severe
Any adverse event	**540 (8.7%)**	**9 (0.1%)**	**232 (4.3%)**	**14 (0.3%)**
Gastrointestinal disorders				
Diarrhoea	47 (0.8%)			
Gen. disorders & admin. site cond.				
Induration	55 (0.9%)			
Irritability	90 (1.4%)		44 (0.8%)	
Malaise	90 (1.4%)		30 (0.6%)	
Pyrexia	58 (0.9%)		47 (0.9%)	
Nervous system disorders				
Crying	40 (0.6%)			
Somnolence	44 (0.7%)			
Psychiatric disorders				
Eating disorders	46 (0.7%)		30 (0.6%)	
Skin & subcutaneous tissue disorders				
Rash	40 (0.6%)			

Source: ISS Tables: Table 45, Table 46, Table 47, Table 48, Table 53, Table 54, Table 55, Table 56

During the infant series of vaccinations, 8.7% (540/6215) of subjects who received MenACWY experienced AEs that were deemed to be possibly or probably related to vaccinations. The majority of these subjects experienced AEs that belonged to the SOC “General Disorders & Administration Site Conditions” and within this category the most common preferred terms were malaise, irritability, pyrexia, and induration. Nine (9) subjects experienced 16 severe AEs that were deemed to be possibly or probably related to MenACWY, the majority of which were solicited events (1 diarrhoea, 1 vomiting, 1 injection site pain, 3 irritability, 1 tenderness, 2 pain in extremity, 1 complex partial seizure, 1 crying, 2 somnolence, 2 eating disorders, and 1 rash). In the 1 month following the first toddler dose, 4.3% (232/5445) of subjects who received MenACWY experienced AEs that were deemed to be possibly or probably related to vaccinations. The most common AEs by preferred term were malaise, irritability, and pyrexia, again all in the category of solicited events. Fourteen (14) subjects (0.3%) experienced 17 severe AEs during this time period that were deemed to be possibly or probably related to the vaccinations (4 diarrhoea, 1 vomiting, 4 irritability, 1 pyrexia, 3 crying, 2 febrile convulsion, 1 somnolence, 1 eating disorder).

For the older infants/toddler subjects, 5.2% (141/2715) of subjects who received MenACWY experienced AEs that were deemed to be possibly or probably related to vaccinations in the 1 month time period following dose 1. The most common preferred terms were irritability, eating disorder, and diarrhea. Six (6) subjects experienced 9 severe AEs that were deemed to be possibly or probably related to MenACWY (1 diarrhoea, 1 vomiting, 1 hyperpyrexia, 1 injection site pain, 2 irritability, 1 tenderness, 1 crying, 1 urticaria). In the 1 month following dose 2, 5.5% (113/2031) of subjects who received MenACWY, experienced AEs that were deemed to be possibly or probably related to vaccinations. The most common preferred terms were irritability and rash. Five (5) subjects (0.2%) experienced severe AEs during this time period that were deemed to be possibly or probably related to the vaccinations (1 pyrexia, 1 viral rash, and 3 eating disorders).

1.3.3.4. Serious adverse events and deaths

Deaths

Five (5) subjects died during the study period in the 8 studies included for the proposed indication (infants/toddlers): 3 in V59P14 (auto accident, lung infection, sepsis of undetermined origin) and in 2 in V59P23 (cardiorespiratory failure probably due to congenital cardiopathy, acute bronchopneumonia). Additional 7 subjects died (6 in study V59P23; septic shock, respiratory failure, sudden death (pneumonitis), cardiac arrest, anomalous pulmonary venous connection, head injury due to fall - and 1 in V59P36; cardiac arrest - were reported to MAH after the interim cutoff) but were outside of the dataset included in this submission. None of the deaths were assessed as possibly or probably related to the MenACWY vaccine.

Serious adverse events

During the infant series 3.0% and 2.6% of subjects experienced any SAEs in the MenACWY and control groups, respectively. In the period between the infant series and the toddler dose 2.6% and 3.0% of subjects experienced any SAEs in the MenACWY and control groups, respectively. Less than 1% of subjects in both groups experienced any SAEs after the toddler dose. For the follow-up period about 1% in both groups experienced any SAEs. The percentages of older infant/toddler subjects who experienced any SAEs 1 month post dose 1 was 0.4% and 0.9% in the MenACWY and MenC groups, respectively. For the infants, the most common SAEs for all 4 time periods included ailments consolidated into a category called “wheezing” followed by “pneumonia”. The older infant/toddler subjects experienced very few SAEs.

Table 32. Summary of Consolidated Serious Treatment-Emergent AEs, by Time Period and Frequency, Infants

	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 (N = 6215)	Control (N = 2508)	ACWY (N = 5771)	Control (N = 2279)	ACWY (N = 5445)	Control (N = 1444)	ACWY (N = 5373)	Control (N = 1164)
Wheezing	58 (0.9%)	22 (0.9%)	41 (0.7%)	23 (1.0%)	3 (0.1%)	2 (0.1%)	15 (0.3%)	5 (0.4%)
Pneumonia	24 (0.4%)	6 (0.2%)	26 (0.5%)	12 (0.6%)	1 (0.0%)	2 (0.1%)	17 (0.3%)	1 (0.1%)
Gastroenteritis	20 (0.3%)	5 (0.2%)	18 (0.3%)	9 (0.4%)	3 (0.1%)	1 (0.1%)	8 (0.1%)	1 (0.1%)
Convulsions	9 (0.1%)	2 (0.1%)	9 (0.2%)	6 (0.3%)	3 (0.1%)	1 (0.1%)	9 (0.2%)	1 (0.1%)
Cellulitis	3 (0.0%)	2 (0.1%)	5 (0.1%)	4 (0.2%)	4 (0.1%)	0	2 (0.0%)	2 (0.2%)
Otitis Media	2 (0.0%)	1 (0.0%)	2 (0.0%)	4 (0.2%)	0	0	0	0
Abscess	2 (0.0%)	2 (0.1%)	5 (0.1%)	2 (0.1%)	2 (0.0%)	0	3 (0.1%)	1 (0.1%)
Allergic reaction	0	0	1 (0.0%)	0	0	0	0	0
Anaemia	0	0	0	1 (0.0%)	0	0	1 (0.0%)	0
Breath holding	2 (0.0%)	1 (0.0%)	0	0	1 (0.0%)	0	0	0

a Consolidated Terms derived from any subject with the following MedDRA Preferred Terms:

A total of 16 suspected related SAEs were reported in the studies contributing to the provided Summary of Clinical Safety, of which 15 were possibly related to MenACWY. These included four cases of febrile convulsion (3 in V59P14, 1 in V59P23), one case of complex partial seizure (V59P14), one case of epilepsy (V59P23), one case of acute disseminated encephalomyelitis (V59P23), groin abscess (V59P23), hospitalisation due to diarrhoea, vomiting and pyrexia (V59P22), pyrexia (V59P23) and three cases of kawasaki's disease (1 in V59P14 and 2 in V59P23). Two possibly related SAEs were reported with the adjuvanted formulations in study V59P5 (supraventricular tachycardia and idiopathic thrombocytopenic purpura).

Kawasaki's disease is discussed in the section on immunological disorders.

1.3.3.5. Laboratory findings

Not applicable.

1.3.3.6. Safety in special populations

Analysis of reactogenicity by gender

Overall, no major differences in the reactogenicity profiles after MenACWY vaccination were observed between the genders in infants and in older infant/toddler subjects. The percentages of subjects who experienced any, any severe, any local, any local moderate and severe, any systemic, any severe systemic, and any other reactions differed by no more than 2% in female and male infant subjects after any vaccination, and no more than 3% in older infant/toddler subjects. Differences between the genders were not unidirectional.

Analysis of reactogenicity by race

There were some differences in the percentages of infant subjects who experienced any reactions when the data was analysed by race, however these were generally small and sample sizes for especially the control groups in the different race strata were relatively small. In older infant/toddler subjects almost all of the subjects who received MenC were Caucasian, making it difficult to compare AE rates by race.

Analysis of reactogenicity by geographic location

After the first vaccination at 2 months, more subjects in both the MenACWY and control groups in Latin America experienced tenderness, erythema, and induration than did the V59P14 US and V59P23 US

subjects. Higher percentages of the LA subjects experienced erythema after the 4-month and 6-month vaccinations. The MenACWY group had a similar or lower incidence of these local reactions compared to the control group, within a study after each vaccination. The percentages of subjects who experienced severe reactions following vaccination at the 4 time periods were low and similar between the groups, although severe tenderness was more commonly experienced in the LA groups than in the US groups following the 2-month and 4-month vaccinations. These differences were not apparent following subsequent vaccinations.

There were differences in the percentages of subjects who experienced any systemic reactions between the US and LA subjects. Overall, fewer LA than US subjects experienced change in eating habits, persistent crying, sleepiness, and irritability. More Latin American subjects experienced rash and fever compared to the US subjects. The percentages of subjects who experienced severe systemic reactions following vaccination were low and similar between the groups within a study as well as across studies.

1.3.3.7. Immunological events

One case of acute disseminated encephalomyelitis (ADEM), an immune mediated disease of the brain, was reported. A 13 month old boy enrolled in study V59P23 developed acute disseminated encephalomyelitis 35 days following receipt of a fourth dose of MenACWY. No evidence was found of an active infection. At the time of preparation for the submission the case had not recovered.

Kawasaki's disease (KD)

There were 7 cases of Kawasaki in the clinical studies for the MenACWY. Of these, 6 occurred in infants/toddlers and one in a 3 year old who received an adjuvanted formulation (>3 months after vaccination). For this latter case, MAH's clinical experts felt the evidence did not support a diagnosis of Kawasaki's disease.

Of the 6 cases in infants three were judged to be possibly related to vaccination, as they occurred within 30 days following vaccination. The remaining cases were not judged to be related as in two cases onset was more than 3 months after vaccination and in one case the subject did not receive MenACWY.

A conservative calculation of the incidence of KD in children up to 2 years of age who received the final formulation of MenACWY in clinical studies is 38 in 100,000 (6 cases in more than 13,000 subject-years of surveillance for all studies). This is not inconsistent with the range of estimates for Kawasaki's disease of between 9 and 100 per 100,000 person-years from surveillance studies[2]. The MAH argued that it should also be considered that the intensity and completeness of surveillance within a vaccine study for adverse events such as Kawasaki's disease might be higher than within routine epidemiologic studies. Other vaccine studies, notably the recent rotavirus prelicensure studies, have identified similar or higher rates of Kawasaki's disease than routine surveillance studies have found. For example, a rate of 54/100,000 with Rotarix has been reported[3].

Finally, higher disease rates are well-known to occur in Asian countries and in children of Asian ancestry. An incidence rate of 146 per 100,000 person-years in infants below 1 year of age is reported from Taiwan[4]. Although only 795 infants of the 7744 subjects from study V59P23 were enrolled in Taiwan, 3 of the 6 cases of Kawasaki's disease were reported from that country.

[2] Newburger, et al., 2004
[3] Pediatric Advisory Board Committee Meeting March 22, 2010
[4] Chang LY, et al., 2004

The MAH conclusion was that considering all the known facts about Kawasaki's disease and the cases from the MenACWY program, including the randomisation ratio of the studies, the lack of consistent temporal relationship to vaccination, the geographical clustering of the cases and the comparison of overall rates to those reported in the literature, this does not represent an increased risk of Kawasaki's disease in MenACWY recipients. According to the MAH, this conclusion was also supported by similar findings obtained in the pivotal registration and post-marketing studies for other recent infant vaccines such as Prevnar, Rotateq, and Rotarix.

1.3.3.8. Safety related to drug-drug interactions and other interactions

No vaccine-vaccine interactions in terms of solicited reactions or unsolicited AEs were observed.

1.3.3.9. Discontinuation due to adverse events

Overall, for the infants 0.7% (40/5563) of subjects in the 4-dose MenACWY group and 0.5% (8/1623) in the 4-dose control group experienced treatment-emergent AEs that led to withdrawal from the study in which they occurred. For the older infants/toddlers, 0.1% (3/2180) of subjects in the 2-dose MenACWY group experienced AEs that led to withdrawal from the study in which they occurred, compared to 0.2% (1/537) in the 1-dose MenACWY group, and 0% (0/229) in the MenC group.

A listing of the possibly/probably related treatment-emergent AEs leading to premature withdrawal from the study is presented in Table 41. All subjects recovered completely from the AEs that led to their withdrawal from the study they were participating in, except for a subject with a case of acute disseminated encephalomyelitis that is gradually improving.

Table 33. Listing of Possibly/probably Related Treatment-emergent Adverse Events Leading to Premature Withdrawal from Study, All Subjects

Study	Age group	Subject	MedDRA Preferred Term (verbatim term)	Severity	Outcome	Relationship
Serious adverse events						
V59P14	Infant	28/7010	Kawasaki's disease (Kawasaki disease)	Severe	Recovered	Possibly related
V59P14	Infant	36/7008	Complex partial seizure (partial complex seizure)	Severe	Recovered	Possibly related
V59P23	Infant	043/0016	Febrile convulsion (febrile seizure)	Severe	Recovered	Possibly related
V59P23	Infant	050/0010	Epilepsy (epilepsy)	Severe	Recovered	Possibly related
V59P23	Infant	121/5028	Acute disseminated encephalomyelitis (acute disseminated encephalomyelitis)	Mild	AE persists	Possibly related
Other adverse events (not serious)						
V59P8	Older infant/toddler	01/08202	Urticaria (Hives)	Severe	Recovered	Possibly related
V59P14	Infant	28/7010	Conjunctivitis (conjunctivitis)	Mild	Recovered	Possibly related
V59P14	Older infant/toddler	53/7010	Irritability (irritability)	Moderate	Recovered	Possibly related
V59P14	Infant	57/5005	Pyrexia (fever)	Mild	Recovered	Probably related
V59P23	Infant	024/0002	Injection site pain (left leg tenderness at injection site)	Moderate	Recovered	Probably related
			Irritability (irritability)	Moderate	Recovered	Possibly related
			Oedema peripheral (left leg swollen)	Mild	Recovered	Probably related
V59P23	Infant	048/5001	Gastroenteritis (gastroenteritis)	Moderate	Recovered	Possibly related

1.3.3.10. Post marketing experience

MenACWY was approved for use in persons 11 years and above on March 15, 2010. MenACWY adverse events cases received by the MAH were analysed for a periodic safety update report (data lock point on 14 March 2011) submitted to European authorities. The evaluations showed no increased frequency of listed reactions, no fatal cases, no drug interactions and no effects on pregnancy or lactation. No vaccine related effect has been evident in any subgroup of vaccinees.

1.3.3.11. Discussion on clinical safety

The provided integrated safety analysis considered 8.932 infants and toddlers aged 2 months to 23 months received the final formulation of MenACWY, which were included in the different studies included in this submission. More subjects in this age group were however exposed, overall only subjects who received the final formulation are considered. Children receiving earlier formulations, including adjuvanted formulations, are not included in this discussion of safety. However, for serious adverse events possibly related to vaccination these will be mentioned.

With regards to reactogenicity, it has to be noted that the majority of MenC subjects were included in study V59P22, where temperature was measured rectally whilst in other studies temperature was measured axillary. So although MenC (menjugate) seems more reactogenic, this could be skewed due to the different measurement methods applied in studies. As expected, reactogenicity decreased with age and with dose.

Although the difference in reported fever between subjects receiving MenC (41%) and MenACWY (12%, 10%) could possibly be explained by a different measurement method applied in study V59P22, the difference with regards to other systemic reactions reported such as diarrhoea, irritability, change in eating habits, sleepiness and persistent crying cannot. In conclusion, reported systemic reactogenicity does appear higher with older infant/toddler subjects receiving MenC as compared to those receiving MenACWY. Systemic reactogenicity also seems lower following the second dose as compared to the first dose.

With regards to possibly or probably related treatment adverse events there is very little difference between the older infants / toddlers and the infants receiving the full infant series.

Kawasaki disease is the most common cause of multisystem vasculitis in childhood, a leading cause of acquired cardiac disease of children in the developed countries. Epidemiologic findings indicate the presence of considerable genetic components in the aetiology; however it is genetically complex, with many genes contributing modest effects to the overall risk, and no single gene “causing” the disease. Specific environmental triggers remain to be identified. Pronounced seasonality and clustering of cases has led to believe an infectious agent is involved. Recent studies indicate a potential role for staphylococcal and streptococcal toxins in the pathology of Kawasaki’s disease, however this remains controversial. Although it cannot be excluded, and Kawasaki has been reported following vaccination, a clear increased risk of Kawasaki’s disease associated with vaccination has not been identified[5], although it is included in the labelling for Rotateq in the US.

Three possibly related cases of Kawasaki disease occurred in the infants included in clinical studies. In their calculations the MAH remained conservative and includes all six cases in infants under the age of two years. This produced an incidence of 38 in 100.000, which the MAH noted to be consistent with reported rates in other vaccine trial settings, referring to the Rotarix trial. It is agreed with the MAH that geographic location is an important factor, and reported rates vary from <10 per 100.000 in the UK to >200 per 100.000 in Japan. In Taiwan the reported rate between 2003 and 2006 was 69 per 100.000, with a peak in summer[6], which is lower than the rate reported by Chang et al (146 per 100.000). Considering this rate it is striking that in the 795 children included from Taiwan, 3 cases of Kawasaki’s disease occurred (a rate of almost 400 per 100.000). This is higher than expected, even for that region. A possible explanation could be the trial setting, and intensive monitoring, however it is thought that an epidemiological study with the aim of estimating the incidence of Kawasaki disease should be able to pick up all the majority of cases as well, especially considering the severity of the disease. It has to be noted that these Taiwanese cases occurred 20 and 149 days after receiving

[5] Harnden et al BMJ 2009, 338:b1514; Wood & Tulloh, Heart 2009;95:787–792.
[6] Huang et al. Pediatrics 2009; 123(3):e401-e405

MenACWY, and the third case did not receive any MenACWY. Therefore only one case considered here is possibly related (in a 12 week old girl who received Infanrix and Prevnar along with MenACWY).

It is agreed with the MAH that there is currently no clear evidence for an increased risk of Kawasaki associated with vaccination with MenACWY. However, the situation should be monitored carefully, especially in areas where subjects seem more genetically disposed to Kawasaki's (such as Japan, Korea, Taiwan etc), as there are few cases that are considered possibly related to vaccination it cannot be excluded that MenACWY is capable of triggering Kawasaki disease.

With regards to discontinuation, the cases leading to discontinuation are limited to the subjects in the studies that are included in the integrated safety analysis of the MAH for this variation application. Not all data of for example study V59P23 is included, and only subjects who received the final formulation have been considered.

1.3.3.12. Conclusions on clinical safety

MenACWY was well tolerated and had a comparable safety profile compared to comparator vaccines in these 8,932 infants and toddlers (12-23 months) included in the provided integrated safety analysis. Expectedly, reactogenicity decreased with age and with dose. 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. There were no increases in adverse events as compared to comparator vaccines included in the different studies. Reported systemic reactogenicity appeared higher following MenC compared to MenACWY in older infants/toddlers.

Except for the cases of Kawasaki disease, there are no other concerns regarding adverse events or serious adverse events.

It is agreed with the MAH that there is currently no clear evidence for an increased risk of Kawasaki associated with vaccination with MenACWY. However, Kawasaki is a serious disease, and based on the current data a potential association with MenACWY cannot be fully excluded. Therefore the situation should be monitored carefully, especially in areas where subjects seem more genetically disposed to Kawasaki's (such as Japan, Korea, Taiwan etc), as there are few cases that are considered possibly related to vaccination it cannot be excluded that MenACWY is capable of triggering Kawasaki disease. Based on available information, update of Product Information or other regulatory action, however, is currently not deemed required.

1.3.3.13. PSUR cycle

The PSUR cycle remains unchanged.

1.3.4. Risk management plan

The MAH submitted an updated Risk Management Plan (version 7.2 of September 2012) within this variation procedure.

Table 34. Summary of the risk management plan

Safety issues	**Agreed Pharmacovigilance Activities (routine and additional)**	**Agreed Risk Minimisation Activities (routine and additional)**
Important identified risks		
Translucent particles in the vial/PFS	Switch from vial/PFS to vial/vial presentation and Package information leaflet)	Switch from vial/PFS to vial/vial presentation and Package information leaflet
Important potential risks		
Guillain-Barré Syndrome	Enhanced pharmacovigilance with use of questionnaire and SMT adjudication, Studies V59_54 and 34	Not applicable
Acute disseminated encephalomyelitis	Enhanced pharmacovigilance with use of questionnaire and SMT adjudication, Studies V59_54and 34	Not applicable
Anaphylactic reactions	Routine pharmacovigilance Studies V59_54and 34	Not applicable
Thrombocytopenia	Routine pharmacovigilance Studies V59_54 and 34	Not applicable
KD and Vasculitis	Enhanced pharmacovigilance with use of questionnaire and SMT adjudication	Not applicable
Brachial neuritis	Routine pharmacovigilance Studies V59_54 and 34	Not applicable
Whole limb swelling	Routine pharmacovigilance	Not applicable
Injection site reactions (severe)	Routine pharmacovigilance	Not applicable
Systemic reactions (severe)	Routine pharmacovigilance	Not applicable
Vaccine failure	Enhanced pharmacovigilance with SMT adjudication	Not applicable
Important missing information:		
Safety of vaccine during pregnancy or lactation	Routine Pharmacovigilance Pregnancy US registry and case control study *"*	SmPC 4.6:" *Insufficient clinical data on exposed pregnancies are available*
Altered immunocompetence subjects	Routine Pharmacovigilance	SmPC 4.4: "*In immunocompromised individuals, vaccination may not result in an appropriate protective antibody response"*
Bleeding disorder subjects	Routine Pharmacovigilance	SmPC 4.4:*"Menveo has not been evaluated in persons with thrombocytopenia, bleeding disorders or that are receiving*

		anticoagulant therapy, because of the risk of haematoma. The risk-benefit ratio for persons at risk of haematoma following intramuscular injection must be evaluated by health care professionals."
Serious acute, chronic or progressive disease patients	Routine Pharmacovigilance	Not applicable
History of Guillain-Barre Syndrome	Routine Pharmacovigilance	Not applicable
Safety and immunogenicity data in elderly	Routine Pharmacovigilance	SmPC 4.2: "*There are limited data in individuals aged 56-65 and there are no data in individuals aged >65 years"*
Exposure to repeated doses, including booster.	Routine parmacovigilance Study V59P20E1 on persistence data Study V59_57 to compare one dose versus two doses in children aged 2 – 10 years Studies in adults evaluating co-administration of Menveo with travelers vaccines:V59-38 and V59_53	Not Applicable
Pediatric subject younger than 2 years of age and off-label usage	Routine pharmacovigilance and monitoring of the number of cases with the HLT "Maladministrations" and PT "Drug administered to patients of inappropriate age" and "Off label use", which will be reported to Health Authorities in the Periodic Update Safety Report (PSUR)	SmPC 4.2: "The safety and efficacy of Menveo in children under 2 years of age has not yet been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made."

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	**Due date**
Study V59_57 to evaluate immediate and longer term antibody titres elicited by one or two doses of Menveo administered in children aged 2-10 years	Final CSR: 4Q 2014
Study V59_34OB, phase IV study to assess the safety of MenACWY in subjects 11 to 20 years of age	Annual updates with PSURs Final CSR: August 2015
Study V59_54OB, phase IV study to assess the safety of MenACWY in a population 2 to 10 years of age	Annual interim reports

Description	Due date
	Annual update with the PSURs Final CSR: December 2015
Study V59P20E1, persistence data study	Final CSR:by end of 2013
Study V59_38, co-administration of Menveo with travellers vaccines	Final CSR: 2Q 2013

The MAH should provide to the CHMP also results of Study V59_53 (co-administration of Menveo with travellers vaccines), which were due by the end of 2012.

1.4. Update of the Product information

Following major objections raised by the CHMP to the initially proposed extension of the therapeutic indication, the MAH change the scope of the variation. Taking into account the requirement to reflect results of studies conducted in line with the agreed PIP, while maintaining the SmPC useful for healthcare professionals and not unduly promotional, the CHMP proposed the following changes to the Product Information (PI), to which the MAH agreed:

Summary of Product Characteristics

4.2 Posology and method of administration

Paediatric population (under 2 years of age)

The safety and efficacy of Menveo in children under 2 years of age has not yet been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.

5.1 Pharmacodynamic properties

Available data in children 2 to 23 months of age

The immunogenicity of Menveo in children 2 to 23 months of age was evaluated in several studies. Although a high percentage of subjects achieved hSBA titres above 1:8 following 4-dose series of Menveo, with lower percentages in studies of 2-dose series and of a single dose, Menveo was compared to another meningococcal vaccine in only one pivotal study, where it failed to show a response at least equivalent to a monovalent conjugated serotype C vaccine (after a single dose at the age of 12 months). Currently available data are not sufficient to establish the efficacy of Menveo in children under 2 years of age. See section 4.2 for information on paediatric use.

Initially proposed changes in SmPC sections 4.4, 4.5 and 4.8 were not supported, as they would be appropriate only in case if extension of the indication was supported.

Changes were also made to the PI to bring it in line with the current QRD template.

2. Benefit-Risk Balance

Benefits

Due to the low incidence rates of MenACWY disease it is not considered feasible to generate clinical efficacy data for licensing, therefore the evaluation of efficacy was based on the measurement of functional antibodies using rSBA and, mainly, hSBA assays. An hSBA titre of 1:4 has been established as a correlate for protection for serogroup C, which is considered a confident measure for clinical protection. From this correlate the value of the immune response for other serogroups is inferred, for which no official correlate has been established.

Beneficial effects

In Europe, cases of meningococcal disease occur sporadically, but occasionally outbreaks can be an important cause of illness and death. Serogroups B and C cause the majority of reported cases in Europe, North and South America, while serogroup A causes the majority of disease in Africa and Asia. The total number of laboratory confirmed cases in the 29 EU/EEA countries of invasive meningococcal disease caused by serogroups A, C, W-135 and Y in the year 2007 was 918 (10 serogroup A, 684 serogroup C, 105 serogroup W-135 and 119 serogroup Y). The fatality rate is highest for serogroup C and Y (14%), as compared to W-135 (7-8%).

An effective vaccine could potentially prevent ~1000 cases of invasive meningococcal disease and save ~125 lives in the EU/EEA countries annually. Menveo also has the potential to protect subjects who travel to other continents against serogroups that are rare in Europe (A and W-135).

The highest incidence of meningococcal disease is seen among infants < 1 year, followed by children 1-4 years. Thus, the potential to save lives and prevent serious disease is especially large in the age group of 2-23 months.

The possible benefits of MenACWY over currently available vaccines are the presence of additional serogroups, in order to provide broader protection (to A, W and Y) in settings where this would be necessary. Secondly, plain polysaccharide vaccines are known to be less effective compared to conjugated vaccines in infants and young children and they do not mount a booster response. After repeated injections the response is less than for the first primary response, a term referred to as hyporesponsiveness. Moreover, plain polysaccharidal MenACWY vaccines are indicated from 2 years onwards only.

The MAH proposed different dosing schedules for infants (2-6 months), older infants and toddlers (6-23 months) and toddlers who are “at risk of exposure”(12-23 months).

For infants aged 2 months four doses at 2, 4, 6 and 12-16 months were proposed. The seroresponse (% with hSBA ≥ 1:8, 95%CI) after four doses was 94% (87,98), 98% (92,100), 100% (96,100) and 100% (96,100) for serogroup A, C, W and Y respectively (PP population, US1a & US2 V59P14).

A 2 dose schedule was proposed for older infants and toddlers (>6 - 23 months). Following one dose given between 6 and 9 months of age, 24-50%, 78-88%, 37-68%, 31-68% of subjects achieved hSBA ≥1:8 for serogroups A,C,W and Y respectively. A second dose given at 12 months increased the response to 88-90%, 96-100%, 96-100%, 92-96% with hSBA ≥1:8. In study V59P14 a first dose of MenACWY given at 12 months of age resulted in a seroresponse (% with hSBA ≥ 1:8) one month after vaccination of 74%, 91% 79% and 72% for serogroup A, C, W and Y respectively. A second dose given at 15 months of age increased the seroresponse to 97%, 100%, 100% and 100% for serogroups A, C, W and Y.

A one dose schedule was proposed for children from 12-23 months of age, in “emergency situations”. The data from different studies show that the response after one dose is moderate and variable between studies ranging from 49-75% for serogroup A, 35-93% for serogroup C, 58-93% for serogroup W, 49-72% for serogroup Y.

In the different phase III trials co-administration with childhood vaccines was evaluated. There was no evidence of clinically relevant interference of MenACWY with diphteria, tetanus, IPV, HBV, and Hib in infants (2-6 months) or with MMRV, Tdap and Hib booster in toddlers.

Persistence of bactericidal antibodies was measured in study V59P14 and study V59P22. Study V59P14 provided data to show persistence for 6 and 10 months. The percentage of US subjects with hSBA≥1:8 six months after their 3rd dose for serogroups A, C, W & Y was 12%, 52%, 69% and 60% respectively. After ten months, in LA subjects, this was 15%, 26%, 63% and 52% respectively. Study V59P22 provided limited persistence data up to 6-18 months (mean: 7 months) for two doses of MenACWY given at 6-8months and 12 months of age (group I), one dose of MenACWY given at 12 months of age (group II) and one dose of Menjugate given at 12 months of age (Group III). The percentage of subjects with hSBA ≥1:8 6-18 months after their last dose for serogroup A was 31% and 7%, for serogroup W 75% and 71%, and for serogroup Y 79% anfd 79% 69% and 60% respectively for group I and II respectively. For serogroup C the percentage with hSBA≥1:8 was 71%, 64% and 54% for group I, II and III respectively, indicating similar or better persistence with MenACWY compared to Menjugate.

There was evidence of the induction of immunologic memory therefore it can be concluded that MenACWY exhibits the characteristics of a glycoconjugate vaccine.

Uncertainty in the knowledge about the beneficial effects

No data on prevention of meningococcal disease have been generated for MenACWY. There is no data on efficacy and safety in children with complement disorders or with functional or actual asplenia.

Non-inferiority of MenACWY to a conjugated monovalent MenC vaccine has not been demonstrated**.** One comparative trial with a conjugated monovalent MenC vaccine (V59P22) failed to demonstrate non-inferiority of MenACWY over the monovalent MenC vaccine. Results of this study were further weakened by identification of GCP issues at one of the sites included in this study, following which results from this site had to be excluded and power of the study decreased.

Across the studies there was considerable variability in the immune response to MenACWY.

There was also seen a risk of subjects being unprotected in the window after the third infant dose and before the fourth dose. The levels of bactericidal antibodies against serogroup A and to some extent serogroup C were rapidly declining in that interval.

In the different phase III trials co-administration with childhood vaccines was evaluated. Co-administration of conjugate pneumococcal vaccine with MenACWY led to a somewhat decreased response to several pneumococcal antigens. The relevance of this decreased response is unknown. With regards to the response to pertussis antigens, non-inferiority of concomitant vaccination with MenACWY to vaccination without MenACWY could not be demonstrated for LA subjects for pertactin only. However, as this could be demonstrated for US subjects, and for PT/FHA, and no statistically significant difference was found considering seroresponse rates, this finding is unlikely to be significant.

Long-term follow up in ongoing clinical studies would provide more persistence data in the future.

There is insufficient comparative data with a monovalent conjugate MenC vaccine demonstrating equal persistence for MenC and no long term persistence data for all serogroups in this age group.

Risks

Unfavourable effects

MenACWY was well tolerated and had a comparable safety profile compared to comparator vaccines in these 8,978 infants and toddlers (12-23 months) included in the integrated safety analysis. As expected, reactogenicity decreased with age and with dose. 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. There were no increases in adverse events as compared to comparator vaccines included in the different studies. Reported systemic reactogenicity appeared higher following MenC compared to MenACWY in older infants/toddlers. Except for the cases of Kawasaki disease, there are no other concerns regarding adverse events or serious adverse events.

Uncertainty in the knowledge about the unfavourable effects

The unfavourable effects, including the reactogenicity, have been precisely described. However, by introducing Menveo in to a larger population including subjects with co-morbidities, rare conditions may occur that could be related to vaccine use.

There is currently no clear evidence for an increased risk of Kawasaki associated with vaccination with MenACWY. However, Kawasaki is a serious disease, and based on the current data a potential association with MenACWY cannot be excluded. Therefore the situation should be monitored carefully, especially in areas where subjects seem more genetically disposed to Kawasaki's (such as Japan, Korea, Taiwan etc), as there are few cases that are considered possibly related to vaccination it cannot be excluded that MenACWY is capable of triggering Kawasaki disease. However, update of the SmPC in this regard is not currently warranted.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Presence of additional serogroups compared to monovalent conjugated meningococcal C vaccines is of limited benefit within the EU, as only very few cases of invasive disease due to serogroups A, W and Y are registered in the EU annually in comparison with cases caused by serogroup C. Protection against these additional serogroups is more important to those children at increased risk of exposure due to travel or in situation of an outbreak. A potential loss in immunity to serogroup C as a result of reduced immunogenicity of MenACWY as compared to conjugated monovalent MenC vaccines would possibly undermine this small gain achieved by adding types A, W and Y. Moreover, it is considered quite important that when a child is vaccinated optimal protection is achieved.

In any case the optimal dosing regimen should be identified, which is especially important in those settings where children are at increased risk of exposure.

The possible risk of Kawasaki disease is considered an important unfavourable effect; however it is not possible to determine whether the association between MenACWY and Kawasaki disease is causal or coincidental.

Benefit-risk balance

Loss in protection against serogroup C should be balanced against the gain achieved by adding types A, W and Y. It is unclear whether optimal protection is achieved under the proposed dosing regimens. Consequently a proportion of vaccinated subjects could be unprotected in their first year of life (i.e. in between the 3rd and 4th dose of the infant schedule), and a relatively large proportion of vaccinated toddlers who are at increased risk of exposure could be unprotected following the single dose recommendation. Therefore, since the above described concerns raised by the CHMP have not been adequately addressed, a positive risk balance in children aged 2 – 23 months cannot be established. Since the efficacy concerns are specific to the age group of 2 – 23 month and no new major safety concerns have been identified, this do not affect the benefit-risk balance in the currently approved indication, which remains positive.

Discussion on the Benefit-Risk Balance

The MAH changed the scope of the requested variation from extension of the indication (to include children aged 2-23 months) to update of the SmPC with results from studies conducted in this age group. Major objections identified through the assessment of this data remain unsolved, however they are specific to the age group of 2-23 months, therefore do not affect the benefit-risk balance in the currently approved indication. It is, however, supported to summarise the available data in section 5.1 of the SmPC, and make corresponding changes in section 4.2.

GCP issues were identified at one of the study sites of study V59P22, following which it was decided to remove the data generated at this site from the final analysis of results. In the agreed PIP it was stated that at least 660 infants would be enrolled and randomized in study V59P22. Due to the GCP issues, data from only 594 infants is included in the analysis, limiting the power of the study. However, the main findings and conclusions of the trial remained unaffected, namely non-inferiority to a monovalent conjugated MenC vaccine could not be demonstrated. Findings from study V59P22 therefore remain valid and should be reflected in the SmPC, and the study still contributes to the PIP. Therefore and The CHMP is of the opinion that the studies conducted are in conformity with the agreed paediatric investigation plan P/93/2011.

Finally, the CHMP concludes that changes to the SmPC as described above are acceptable.

3. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation requested		**Type**
C.I.4	Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

Update of sections 4.2 and 5.1 of the SmPC to reflect available data in children aged 2-23 months. Furthermore, the PI is being brought in line with the latest QRD template version 9.0.

The requested variation proposed amendments to the SmPC and Package Leaflet.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/93/2011 and the results of these studies are reflected in the Summary of Product Characteristics.