24 April 2012

EMA/332810/2012

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/0017

Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

15 March 2012
EMA/CHMP/169208/2012
Committee for Medicinal Products for Human Use (CHMP)

CHMP Type II variation assessment report

Invented name Menveo

Procedure No. EMEA/H/C/001095/II/0017

Marketing authorisation holder (MAH): Novartis Vaccines and Diagnostics S.r.l.

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

1. Scientific discussion

1.1. Introduction

Invasive meningococcal infection is caused by Neisseria meningitides, a strictly human pathogen.

Meningococcal meningitis, the most common pathological presentation of invasive meningococcal disease, is characterised by fever, headache and stiff neck and may have long-term sequelae such as mental retardation, sensor neural hearing loss, and seizure disorders. Meningococcemia is less common but has a high mortality rate even when treated.

Onset of disease is usually very rapid with signs of fever, shock, embolic rash, disseminated intravascular coagulation and multiorgan failure. Other common presenting signs of meningococcal disease are vomiting, lethargy, irritability, poor feeding, cough or rhinorrhea and seizures. Complications include arthritis, myocarditis, pericarditis, endophthalmitis or pneumonia and may result in long term sequelae such as skin necrosis requiring grafts, limb necrosis requiring amputation, and chronic renal failure. Less common meningococcal diseases include pneumonia, occult febrile bacteraemia, conjunctivitis and chronic meningococcemia.

The mortality rate of meningococcal disease is still approximately 10% in both developing and industrialised countries. According to WHO there are approximately 1.2 million cases per year causing an estimated 135,000 deaths.

Thirteen meningococcal serogroups are currently recognised, based on the immunochemistry of the capsular polysaccharide. For epidemiological purposes, a further classification system exists, which divides strains immunologically into serotypes, serosubtypes and immunotypes, based on antigenic differences in the PorB OMP, PorA OMP, and lipo-oligosaccharides (immunotypes), respectively.

Serogroups A, B, C, W-135 and Y are the most common causes of invasive meningococcal disease worldwide and serogroups A, B and C account for the vast majority of these cases (~90%). There are geographical differences and in Europe and Latin- America the dominant serogroups which cause disease are B followed by C. In United States B, C and Y dominate, while serogroup A is the major cause of meningococcal disease in Asia and Africa. However, the epidemiology of meningococcal disease is dynamic over time and the relative importance of the different serogroups fluctuates. An increase in serogroup Y disease has recently been observed in the Finland, Norway and Sweden and are now causing 12%, 7% and 20% of the meningococcal cases, respectively. In the other European countries serogroup Y appears in the range of 0-4% of cases. A similar increase in serogroup Y cases has been seen in United States where serogroup Y disease was uncommon, accounting for only 2% of cases in 1989-1991. By mid-1990s one third of the cases were caused by this serogroup. In Africa serogroups W-135 have emerged as an important cause of epidemic meningitis. This serogroup has previously been relatively uncommon globally.

The incidence of meningococcal disease is highest in the youngest age groups (<1-4 years of age). However, older children, adolescents and adults are more often affected during epidemics. Asplenic persons, individuals with complement deficiencies and people living in close proximity to others (e.g. college/university students and military recruits) have an increased risk of developing meningococcal disease.

Nasopharyngeal colonisation by meningococci is relatively common and is generally asymptomatic, but only a small percentage of colonised persons develop disease. Carriage rates vary with age with lower carriage rates being reported in young children and the highest rates in young adults. Once an individual has become colonised with *Neisseria meningitidis*, the likelihood of acquiring invasive meningococcal disease depends on the virulence of the particular organism, host factors affecting

innate susceptibility, and the presence or absence of serum antibodies capable of activating complement-mediated bacteriolysis and clearing of the organism from the blood stream.

The precise mechanism of immunity to meningococci is unknown, although it is thought to involve a complex interaction between innate and acquired immunity. Nevertheless, humoral immunity is thought to play a central role in host defence against *N. meningitidis* through complement mediated killing induced by antibodies towards both the capsular polysaccharide and sub-capsular structures.

The polysaccharide capsules of *N. meningitidis* are important determinants of virulence. The capsular polysaccharides protect the meningococcus from desiccation, opsonisation, phagocytosis and complement-mediated bactericidal killing as well as aiding in transmission and colonisation.

Plain polysaccharide vaccines have been available for protection against MenA, C, W-135 and Y for several decades but they are poorly or not at all immunogenic in young children, they do not elicit immune memory and they can cause hyporesponsiveness to repeated doses, especially for group C. Conjugate vaccines that employ appropriate protein carrier molecules have the potential to overcome these problems. Hence, two conjugated quadrivalent meningococcal conjugate vaccines are already approved in some countries. These are Menactra (conjugated to diphtheria toxoid; authorised for use in 2 to 55 year-olds in the USA, Canada and Gulf States) and Menveo (conjugated to CRM_{197}) which was approved for use in the EU in March 2010 as a single dose for use from 11 years of age and has also been authorised 11 to 55 years in Canada and Australia and 2 to 55 years in the US.

1.2. About the product

Menveo is a quadrivalent meningococcal conjugate vaccine containing serogroups A, C, W, and Y (henceforth referred to as MenACWY). MenACWY uses pre-sized oligosaccharides from each of the primary pathogenic serogroups (A, C, W, 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 was authorised in March 2010 and is currently indicated for active immunization of adolescents (from 11 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. The additional immediate packaging for MenCWY liquid finished product (3mL glass vial with a 13 mm stopper and flip-off) in addition to the initially approved syringe was authorised in March 2011 (multidose package consisting of 5 MenA Lyo vials and 5 MenCWY liquid vials). In April 2011, a new presentation of single-dose vial-vial package was also authorised.

1.3. The development programme/compliance with CHMP guidance/scientific advice

CHMP Scientific Advice was sought on several occasions to discuss the clinical development of Menveo, including the development in children from 2 to 10 years of age.

Prior to the first submission in 2008, the CHMP answers concerning the clinical questions confirmed that:

- The use of human serum complement in the SBA test and SBA titer of ≥ 1:4 is acceptable as a surrogate measure of protection. A titer of 1:4 is considered seropositive.

- Standardisation of the SBA test should be extensively discussed, like the influence of strain of *N. meningitidis* used in the assay and other parameters.

- The importance of differentiating between subjects who are seropositive or seronegative at baseline for the analysis of non-inferiority versus comparator vaccine. The vaccine response should be defined as seroconversion of initially seronegative subjects or as a four-fold increase in antibody titer among initially seropositive subjects.

- Investigations of immunological aspects as persistence of antibodies, response to carrier protein and vaccination with conjugate vaccine following vaccination with plain polysaccharide, as described by WHO recommendations for MenA and Men C vaccines should be considered.

For the clinical program in the 2 to 10 years of age population, the CHMP answers concerning the clinical questions confirmed that:

- The safety database was considered acceptable in accordance with the guideline on clinical evaluation of new vaccines

- A quadrivalent meningococcal polysaccharide vaccine (i.e. Menomune) was not considered the best available comparator. Accordingly, a new study in children 2 to 10 years of age (V59P20, conducted in the United States and Canada) which compared Menveo to another quadrivalent meningococcal conjugate vaccine (Menactra) was included in the Menveo clinical development plan. The CHMP considered MenC conjugated vaccines as an adequate comparator for this age group.

- In line with the conjugated MenC experience vaccines in EU, it was expected to demonstrate that Menveo is superior to the meningococcal polysaccharide and that justification for using non-inferiority in V59P10 study should be provided. CHMP further noted that even a 10% difference in immunogenicity might not be acceptable (non-inferiority approach) as reduction in immunogenicity could affect the herd immunity and be clinically relevant.

- For the 2-5 years age group the duration of protection is at least as important as insight into the primary response.

Subsequent to CHMP advice there were also a pre-submission meeting with the Rapporteur, co-Rapporteur and EMA in March 2011 to discuss the clinical data prior to submission. The Rapporteur commented that while the proposed plan was suitable for an extension of the current indication to the 2 to 10 years population there could be a limitation for a routine use recommendation due to the lack of head-to-head study versus a MenC vaccine.

1.4. General comments on compliance with GMP, GLP, GCP

GMP

The production facilities are major manufacturing sites for the MAH and have current GMP certificates.

GLP

Safety and toxicology studies were GLP compliant.

GCP

The Clinical Overview and the individual study reports carry statements regarding compliance with GCP guidelines operative at the time that each study was conducted. Clinical trials outside EU were performed according to ethical standards of Directive 2001/29/EC.

1.5. Type of application and other comments on the submitted dossier

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Vaccines and Diagnostics S.r.l. submitted to the European Medicines Agency on 8 August 2011 an application for a type II variation.

The present type II application EMEA/H/C/1095/II/17 has the purpose to expand the age indication of Menveo, meningococcal ACWY conjugate vaccine (diphtheria CRM_{197} conjugate) to include children from 2 to 10 years of age inclusive.

The **proposed indication** is:

> *Menveo is indicated for active immunization of children (**2 years of age and above**), adolescents 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 **proposed posology** is:

> *In children (**from 2 years of age and above**), adolescents (from 11 years of age) and adults Menveo should be administered as a single dose (0.5 ml).*

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/93/2011 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/93/2011 was completed.

The PDCO issued an opinion on compliance for the PIP P/93/2011.

2. Scientific overview and discussion

2.1. Quality aspects

MenACWY as currently authorised is presented as a prefilled syringe or a vial (liquid solution of the MenCWY component) and vial (lyophilized powder of the MenA component).

Presence of oily and translucent visible particles has been detected in the syringes and communicated to the EMA in February 2011. Analyses of these particles revealed that they are composed by silicone oil and proteins. Based on the provided information it was concluded that these particles had been present in the pre-filled syringe drug product all along, and from a pharmacological-toxicological point of view the presence of polydimethylsiloxane did not raise a serious concern, therefore it was judged that no immediate action needed to be taken. Further information about this aspect is provided in the

sub-section on 'Translucent particles in the syringe/vial formulations procedure' under the risk management plan section.

2.2. Non-clinical aspects

Toxicological evaluations of process residual levels throughout the development of the manufacturing process for Menveo have played a role in the finalisation of specifications for drug substances and drug products. In 2005, prior to the finalisation of manufacturing specifications, the toxicological impact of the maximal theoretical amounts of each chemical residue per dose was described in a technical report (Toxicological evaluation of the acceptance criteria for the residues of chemicals in the drug substances of Meningococcal ACWY conjugate vaccine).

Sixteen manufacturing residuals have been re-evaluated in the context of the 2-10 age group.

Following standard toxicological practices, for each residual, the most conservative dose of compound associated with toxicity in a species (usually expressed on the basis of mg/kg of body weight) was selected as the starting point of the assessment.

The toxicity values used for calculations of the maximal theoretical mounts of residuals per dose were obtained from the available toxicology literature and/or allowable limits set by guidelines or regulatory agencies. The safety multiples were calculated for a 7kg individual. The MAH concludes that the safety multiples are adequate to support the safety of an intramuscular injection of a 0.5 mL dose of the MenACWY.

Discussion on non-clinical aspects

The MAH has recalculated the limits for the impurities of 16 different chemicals that are used in manufacturing the Menveo product. The MAH has evaluated the maximum concentrations based on acceptance criteria, and has related this also to the possible dose to children at a weight of 7kg.

The MAH did not discuss the possibility that the limits applied thus far for vaccines intended to be used in adults might not be applicable to the use in children. However, based on the levels of residuals, and the acceptable levels, the safety multiples remain in the order of > 50× and higher for most of the other compounds. Applying an additional arbitrary safety factor of 10 results in lower safety margins, but the margins are still acceptable.

Conclusion on non-clinical aspects

From a toxicological viewpoint there is no objection to the limits proposed for residuals.

2.3. Clinical aspects

An overview of studies submitted in context of this type II variation, and studies submitted and assessed earlier but thought to be relevant to the current variation application, is presented in table 1.

Table 1: Overview of submitted clinical studies

Study ID	Geographic Location	Study Objective (Primary)	Design	Test Product(s); Dosage Regimen; Route of Administration	Subjects by arm	Age groups included	Presentation
PHASE II STUDIES							
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	
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)	Vial/Vial
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)	Vial/Vial

V59P10	Argentina	Safety & Immune Response of One Dose MenACWY vs. Menomune	Observer-Blind, Randomized, Active Controlled Phase 3 Multi-Centre	• MenACWY • Menomune SC	• 949 • 551	Children (2-10 years)	Vial/Vial
PHASE III STUDIES							
V59P20	US Canada	Safety & Immune Response of MenACWY vs. Menactra	Observer-Blind, Randomized, Active Controlled Phase 3 Multi-Centre	• MenACWY • Menactra	• 1635 • 1263	Children (2-10 years)	Vial/Syringe

Clinical efficacy

Dose-response studies and main clinical studies

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, V59P5, 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 Menjugate. 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.

Additional phase 2 **study V59P5** conducted in infants also supported the final dose composition of the MenACWY vaccine, and confirmed that the adjuvant was not required.

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. Further information on V59P7 is also provided under the section 'supportive studies'.

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

Main clinical studies

V59P20 is a phase 3, randomised, observer-blind, multicenter study conducted in the US and Canada in children 2-10 years of age to compare the safety and immunogenicity of MenACWY with Menactra.

Methods

- **Study Participants**

Healthy male and female subjects aged 2 – 10 years who were up to date with age-appropriate routine childhood vaccinations, available for all visits/calls and for whom informed consent was available were included. Children with previous or suspected disease caused by *N. meningitidis* or who had a household contact/intimate exposure to an individual with proven *N. meningitidis* infection within 60 days prior to enrollment, or who had previously been immunized with a meningococcal vaccine/ meningococcal antigens were excluded.

- **Treatments**

Subjects were randomised to receive one single 0.5 mL dose of MenACWY or one single 0.5 mL dose of Menactra (manufactured by Aventis Pasteur Inc., Swiftwater, PA) (meningococcal A, C, Y, and W-135 polysaccharides conjugated to approximately 48 µg of diphtheria toxoid protein carrier).

- **Objectives**

Primary Objectives

- To compare the immunogenicity of a single dose of MenACWY with the immunogenicity of a single dose of Menactra, defined as percentage of subjects with seroresponse directed against *N. meningitidis* serogroups A, C, W-135, and Y, at 1 month after vaccination, when administered to healthy children 2 to 5 years of age.
- To compare the immunogenicity of a single dose of MenACWY with the immunogenicity of a single dose of Menactra, defined as percentage of subjects with seroresponse directed against *N. meningitidis* serogroups A, C, W-135, and Y, at 1 month after vaccination, when administered to healthy children 6 to 10 years of age.

Secondary Objectives

- To assess the immunogenicity of two doses of MenACWY, administered 2 months apart, and compare it to the immunogenicity of a single dose of MenACWY, defined as percentage of

subjects with seroresponse, hSBA ≥ 1:4, hSBA ≥ 1:8 and hSBA GMTs directed against N. meningitidis serogroups A, C, W-135, and Y, at 1 month after vaccination, when administered to healthy children 2 to 5 years of age;

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

Safety Objectives

- To describe the safety profile of MenACWY and to compare the percentages of subjects in the MenACWY and Menactra vaccine groups when administered to healthy children 2 to 10 years of age in terms of immediate hypersensitivity reactions (within 30 minutes) following vaccination, local and systemic reactions during days 1 – 7 after vaccination, adverse events during the time periods pre-defined, medically significant AEs for the duration of the study and serious adverse events (SAEs) for the duration of the study.

- **Outcomes/endpoints**

The primary variable was the percentage of subjects with seroresponse to vaccination in the per protocol population. As a sensitivity analysis, the primary endpoint was also evaluated for the Modified Intention-To-Treat (MITT) population.

Endpoints for immunogenicity evaluation:

1 month post-vaccination (primary):

- hSBA seroresponse to one dose of MenACWY or Menactra
  - in 2-5 year olds
  - in 6-10 year olds

1 month post-vaccination (secondary):

- seroresponse, hSBA ≥ 1:4 and ≥ 1:8, GMTs to 1 dose of MenACWY or Menactra
  - in 2-10 year olds
- hSBA ≥ 1:4 and ≥ 1:8, GMTs to 1 dose of MenACWY or Menactra
  - in 2-5 year olds
  - in 6-10 year olds
- seroresponse, hSBA ≥ 1:4 and ≥ 1:8, GMTs to 2 doses of MenACWY
  - in 2-5 year olds

Seroresponse is a composite endpoint defined as follows:

If Baseline Titre is:	Then Seroresponse is:
Pre-vaccination titre **< 1:4**	Post-vaccination titre **≥ 1:8**
Pre-vaccination titre **≥ 1:4**	Post-vaccination titre fourfold increase over baseline

- **Sample size**

The power for this study was based on the estimate of the percentage of subjects with seroresponse within each serogroup as observed in the previous V59P8 study in children ages 2-10 years.

- **Randomisation**

The randomisation was stratified by age with the following targets per age strata: children 2 to 5 years of age (n = 1700), and children 6 to 10 years of age (n = 1120). In the 2 to 5 years of age group, subjects were to be randomised in a 1:2:2 ratio to receive either two doses of MenACWY, one dose of MenACWY, or one dose of Menactra. The subjects 6 to 10 years of age were to be randomised in a 1:1 ratio to receive a single dose of either MenACWY or Menactra.

- **Blinding (masking)**

The trial was designed as an observer-blind study except for those subjects in Group I who were administered two doses of MenACWY in an open-label fashion.

- **Statistical methods**

Analysis populations

Randomised population: The randomised population contained all subjects enrolled and randomised in the study. These were subjects who had a signed informed consent, were enrolled into the study and randomised. This population was used for the analysis of demographics and all subject listings.

Exposed population: Subjects who actually received a study vaccination were included in the Exposed Population. Should there have been an error in administration where the actual vaccination that the subject received was different than the one to which they were randomly assigned, the subject was included in the vaccination group for the treatment received.

Safety population: All subjects who received the study vaccination and had post-baseline safety data were included in the safety analysis. This population was used for the analysis of local and systemic reactions and other adverse events. As described for the Exposed population, subjects were included in the group for the vaccination actually received.

Modified Intention-to-treat (MITT) population, Immunogenicity: The MITT population included all subjects who received a study vaccination and provided an evaluable serum sample both before and after vaccination. Should there have been an error in administration where the actual vaccination that the subject received was different than the one to which they were randomly assigned, the subject was included in the vaccination group for the treatment to which they were randomised ('analysed as randomised'). The MITT population was summarized and used to evaluate only the primary endpoints.

Per protocol (PP) population, Immunogenicity: The PP population for immunogenicity analysis included all subjects in the MITT population who provided evaluable serum samples (titer results were available) both before and after vaccination and had no major protocol deviation, as defined prior to unblinding. This population was used to evaluate all the primary and secondary immunogenicity objectives.

Analyses

Within each age group, the 95% CIs for the difference in proportions (given serogroup for MenACWY – given serogroup for Menactra) was constructed using standard methods. Immunogenicity of MenACWY was considered non-inferior to the immunogenicity of Menactra, for each of the four serogroups, if the lower limit of the two-sided 95% confidence interval (CI) for the difference between the groups (MenACWY group minus Menactra group) in the percentage of subjects with hSBA seroresponse for that serogroup was greater than -10%. Moreover, if the CI was entirely to the right of 0%, then superiority was declared. The combined hypothesis testing for non-inferiority and statistical superiority did not require any adjustment for multiplicity.

Results

- **Participant flow**

A total of 2907 subjects from 67 study centers were enrolled and randomised (359 in the MenACWY 2-dose group, 1278 in the MenACWY group and 1270 in the Menactra group), while 2898 subjects were vaccinated (356 in the MenACWY 2-dose group, 1279 received MenACWY and 1263 were administered Menactra).

Figure 1: Subject Disposition Flowcharts (Ages 2 to 5)

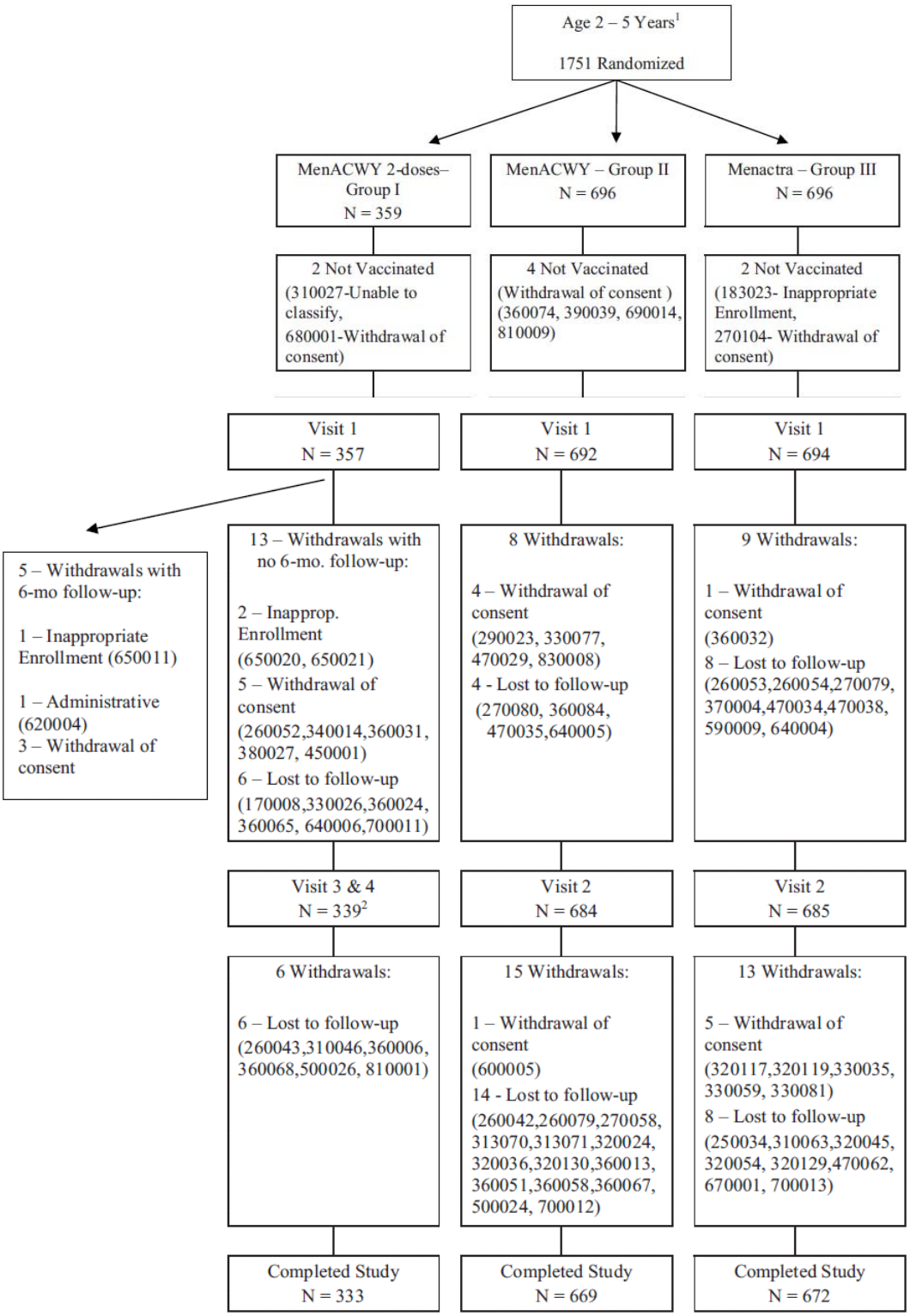
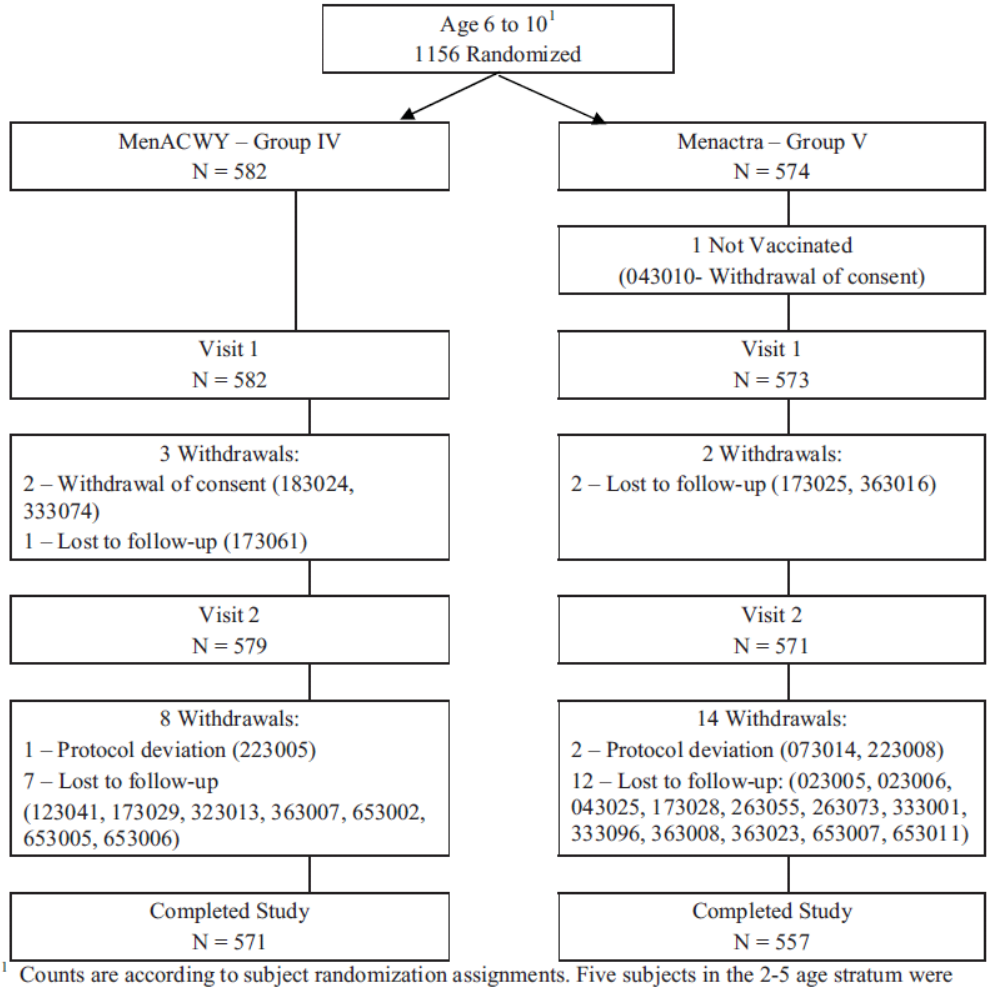


Figure 2: Subject Disposition Flowcharts (Ages 6 to 10)



[1] Counts are according to subject randomization assignments. Five subjects in the 2-5 age stratum were randomized into the 6-10 age stratum in error. These subjects are analyzed with the 2-5 age stratum for all analyses.

- **Recruitment**

The first subject was enrolled on 13 March 2008, the last visit was completed on 14 October 2009.

- **Conduct of the study**

In total 646 subjects had protocol deviations during the conduct of the study (144 [40%] in the MenACWY 2-dose group, 258 [20%] in the MenACWY group and 244 [19%] in the Menactra group).

The most common deviation among the major protocol deviation was "No post-vaccination blood draw" with 130 subjects (38 [11%] in the MenACWY 2-dose group, 44 [3%] in the MenACWY group and 48 [4%] in the Menactra group), followed by "No pre-vaccination blood draw" with 60 subjects (6 [2%] in the MenACWY 2-dose group, 29 [2%] in the MenACWY group and 25 [2%] in the Menactra group), and "Post-vaccination blood draw out of window" with 37 subjects (7 [2%] in the MenACWY 2-dose group, 13 [1%] in the MenACWY group and 17 [1%] in the Menactra group). A total of 20 subjects were enrolled who did not satisfy the entry criteria. Twenty subjects received the wrong vaccine or an

incorrect dose. One additional subject was not vaccinated because of an entry criteria violation discovered post-randomisation.

- **Baseline data**

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

Table 2: Demography and Other Baseline Characteristics - All Randomised Population

		2 – 5 Years			6 – 10 Years		2 – 10 Years	
		MenACWY 2-doses	MenACWY	Menactra	MenACWY	Menactra	MenACWY	Menactra
		(N=359)	(N=696)	(N=696)	(N=582)	(N=574)	(N=1278)	(N=1270)
Mean age Years (SD)		3.5 (1.1)	3.5 (1.1)	3.5 (1.1)	7.9 (1.4)	8.1 (1.4)	5.5 (2.5)	5.6 (2.6)
Female N (%)		171 (48%)	342 (49%)	331 (48%)	280 (48%)	249 (43%)	622 (49%)	580 (46%)
Race: N (%)								
	Asian	19 (5%)	36 (5%)	25 (4%)	31 (5%)	34 (6%)	67 (5%)	59 (5%)
	Black	44 (12%)	89 (13%)	94 (14%)	79 (14%)	81 (14%)	168 (13%)	175 (14%)
	Caucasian	220 (61%)	419 (60%)	425 (61%)	387 (66%)	378 (66%)	806 (63%)	803 (63%)
	Hispanic	55 (15%)	107 (15%)	98 (14%)	40 (7%)	39 (7%)	147 (12%)	137 (11%)
	Other	21 (6%)	45 (6%)	54 (8%)	45 (8%)	42 (7%)	90 (7%)	96 (8%)
Mean Weight in kg (SD)		17.40 (4.05)	17.37 (4.02)	17.35 (3.88)	31.90 (10.06)	31.19 (9.78)	23.99 (10.36)	23.62 (9.95)
Mean Height in cm (SD)		102.04 (10.00)	102.13 (10.08)	102.31 (9.87)	131.03 (11.01)	131.45 (10.74)	115.31 (17.83)	115.54 (17.78)
Met study criteria		350 (97%)	680 (98%)	681 (98%)	572 (98%)	569 (99%)	1252 (98%)	1250 (98%)

- **Numbers analysed**

In total, 2907 subjects were enrolled and 2802 subjects completed the study.

Table 3: Numbers analysed

	2 – 5 Years			6 – 10 Years		2 – 10 Years	
	MenACWY 2-doses	MenACWY	Menactra	MenACWY	Menactra	MenACWY	Menactra
Population:							
Randomized	359	696	696	582	574	1278	1270
Exposed	356	696	691	583	572	1279	1263
Safety	351	693	684	582	571	1275	1255
Safety - 6 Month Follow-up	335	672	675	573	558	1245	1233
MITT	315	636	641	565	557	1201	1198
Per Protocol	297	616	619	554	542	1170	1161

- **Outcomes and estimation**

MenACWY vs Menactra

The primary objective of study V59P20, assessed 1 month after a single vaccination, was to compare the immunogenicity (% with seroresponse) of a single dose of MenACWY with the immunogenicity of a single dose of Menactra in healthy children aged 2 to 5 years (a) and aged 6 to 10 years (b).
In children aged 2 to 5 years, the percentage of seroresponders at 1 month postvaccination was higher in the MenACWY group than in the Menactra group for serogroups C (60% vs. 56% for MenACWY and Menactra, respectively), W (72% vs. 58%), and Y (66% vs. 45%), but lower for serogroup A (72% vs. 77%). Non-inferiority criterion was met for serogroups C, W and Y but not for serogroup A. In children aged 6 to 10 years, the percentage of seroresponders was higher in the MenACWY group than in the Menactra group for serogroups C (63% vs. 57%), W (57% vs. 44%), and Y (58% vs. 39%), but lower for serogroup A (77% vs. 83%). The non-inferiority criterion was met for serogroups C, W and Y, but not for serogroup A. Statistical superiority of MenACWY over Menactra for serogroup W and Y was observed in both age groups. Results were similar in the MITT population.

Table 4: Percentage of Subjects with hSBA Seroresponse at 1 Month Postvaccination (95% CI) by Age Group, PP Population

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

As a secondary objective the seroresponse between the two vaccines was compared for the whole population combined (i.e. 2-10 years). Similarly as for the primary objective, the % seroresponders was higher in the MenACWY group as compared to the Menactra group for all serogroups except A. Non-inferiority in this case could be demonstrated for all serogroups. Similar results were observed for the percentage of subjects with hSBA ≥ 1:4 and ≥ 1:8.

Table 5: Secondary Immunogenicity Objective: Percentage of Subjects with hSBA ≥1:8 at Day 1 and Day 29, Children 2 to 5 and 6 to 10 years of age, PP Population

		2 – 5 Years			6 – 10 Years		
		MenACWY	Menactra	Vaccine group difference (95% CI)	MenACWY	Menactra	Vaccine group difference (95% CI)
Day 1	A	9 (1%) (1-3) N=606	11 (2%) (1-3) N=611	(0%) (-2-1)	13 (2%) (1-4) N=551	9 (2%) (1-3) N=541	1% (-1-3)
	C	61 (10%) (8-13) N=607	57 (9%) (7-12) N=615	(1%) (-3-4)	131 (24%) (20-27) N=554	128 (24%) (20-28) N=539	0% (-5-5)
	W	143 (24%) (21-28) N=594	130 (21%) (18-25) N=605	(3%) (-2-7)	254 (47%) (43-51) N=542	235 (44%) (40-48) N=533	3% (-3-9)
	Y	81 (14%) (11-17) N=593	81 (14%) (11-16) N=600	(0%) (-4-4)	170 (31%) (27-35) N=545	158 (29%) (26-33) N=539	2% (-4-7)
Day 29	A	436 (72%) (68-75) N=606	475 (78%) (74-81) N=611	(-6%) (-11--1)	426 (77%) (74-81) N=551	451 (83%) (80-86) N=541	-6% (-11--1)
	C	413 (68%) (64-72) N=607	392 (64%) (60-68) N=615	(4%) (-1-10)	426 (77%) (73-80) N=554	397 (74%) (70-77) N=539	3% (-2-8)
	W	532 (90%) (87-92) N=594	453 (75%) (71-78) N=605	(15%) (11-19)	494 (91%) (88-93) N=542	448 (84%) (81-87) N=533	7% (3-11)
	Y	448 (76%) (72-79) N=593	341 (57%) (53-61) N=600	(19%) (14-24)	433 (79%) (76-83) N=545	341 (63%) (59-67) N=539	16% (11-21)

Source: Table 14.2.1.7, Table 14.2.1.8

For subjects aged 2-10 years, pre-vaccination GMTs were similar between the two vaccine arms. At day 29, the GMTs showed a large increase for all four serogroups in both vaccine groups but were consistently higher in the MenACWY group for serogroups C, W, and Y (C: 23 vs. 17 in the MenACWY and Menactra groups, respectively, W: 49 vs. 26, Y: 29 vs. 12) and were similar for serogroup A (A: 30 vs. 29). MenACWY was non-inferior to Menactra for all four serogroups (see table 6 below).

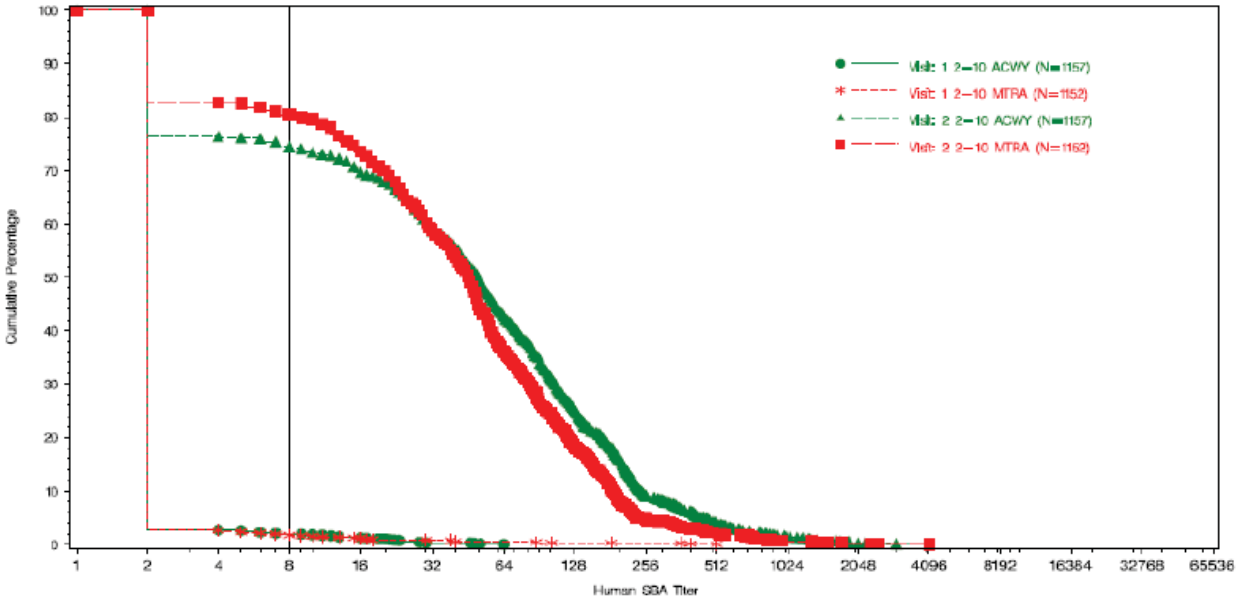
Table 6: Secondary Immunogenicity Objective: hSBA GMTs at Day 1 and Day 29, Children 2 to 10 Years of Age, PP Population

		MenACWY	Menactra	Vaccine Group Ratio (95% CI)
Day 1	A[a]	2.1 (2.05-2.15)	2.11 (2.05-2.16)	1 (0.97-1.03)
	C[b]	3.14 (2.96-3.32)	3.06 (2.89-3.24)	1.02 (0.96-1.1)
	W[c]	5.2 (4.7-5.74)	4.73 (4.28-5.23)	1.1 (0.97-1.24)
	Y[d]	3.5 (3.26-3.77)	3.36 (3.12-3.62)	1.04 (0.96-1.14)
Day 29	A[a]	30 (27-34)	29 (26-33)	1.03 (0.89-1.18)
	C[b]	23 (21-27)	17 (15-20)	1.34 (1.15-1.56)
	W[c]	49 (44-54)	26 (23-29)	1.87 (1.65-2.12)
	Y[d]	29 (25-32)	12 (11-14)	2.37 (2.06-2.73)

Source: Table 14.2.1.17
[a] serogroup A: MenACWY N=1157, Menactra N=1152
[b] serogroup C: MenACWY N=1161, Menactra N=1154
[c] serogroup W: MenACWY N=1136, Menactra N=1138
[d] serogroup Y: MenACWY N=1138, Menactra N=1139

For the 2-5 age group, as well as for the 6-10 age group and the combined ages, the reverse cumulative distribution curves for MenACWY and Menactra cross. Thus, although the percentage of subjects with an hSBA ≥ 1:8 post-vaccination did not meet the non-inferiority criteria when comparing MenACWY to Menactra, among those that did achieve positive titers, the titers were higher after MenACWY. This can be seen in the RCDF curves where the MenACWY group has a longer "tail" than Menactra (RCDC for serogroup A shown, for combined age groups).

Figure 3: Reverse cumulative distribution of Men A human compliment SBA titers before and 1 month after 1st dose by serogroup (Age 2 to 10 years) –PP population



2 doses vs 1 dose of MenACWY

In children aged 2 to 5 years the seroresponse, % with hSBA ≥1:8 and GMT's after 2 doses with MenACWY was compared with the seroresponse, % with hSBA ≥1:8 and GMT's following a single dose (one month post vaccination). Results are presented in the following table:

Table 7: Secondary Immunogenicity Objective: Percentage of Subjects with hSBA Titer≥1:8 and GMTs of Subjects at Day 1 and at One Month Post-Vaccination, Children 2 to 5 years of age (2 doses v/s 1dose), PP Population

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

Source: Table 14.2.1.6, Table 14.2.1.10, Table 14.2.1.18; * p < 0.05, ** p < 0.01, *** p < 0.001, NA = Not applicable.
[a] serogroup A: MenACWY 2 Doses N=291, MenACWY 1 Dose N=606
[b] serogroup C: MenACWY 2 Doses N=293, MenACWY 1 Dose N=607
[c] serogroup W: MenACWY 2 Doses N=288, MenACWY 1 Dose N=594
[d] serogroup Y: MenACWY 2 Doses N=286, MenACWY 1 Dose N=593

The percentages of seroresponders was consistently higher in the MenACWY 2-dose group than in the MenACWY single dose group for all four serogroups (A 91% vs. 72%, C: 98% vs. 60%, W: 89% vs. 72%, and Y: 95% vs. 66%). At one month post-vaccination, the percentages of subjects with hSBA ≥1:8 showed a large increase for all four serogroups in both vaccine groups but were consistently higher for all four serogroups in the MenACWY 2-dose group (A: 91% vs. 72%, C: 99% vs. 68%, W: 99% vs. 90%, and Y: 98% vs. 76%). Similar results were observed for the percentage of subjects with hSBA≥1:4. At day 29, the GMTs showed a large increase for all four serogroups in both vaccine groups but were significantly higher for all four serogroups in MenACWY 2-dose group (A: 64 vs. 27, C: 144 vs. 18, W: 132 vs. 41, and Y: 102 vs. 23).

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Clinical studies in special populations

N/A

Supportive study

Study V59P7

V59P7 was a phase 2, randomised, observer-blind, multicenter, active-controlled study conducted in Finland and Poland during 2005-2006 in children aged 1-5 years. A total of 623 subjects were enrolled and randomised into one of four vaccination groups according to their age. Toddlers aged 12-35 months were randomised to MenACWY (N = 206) or MenACWY adjuvant-containing (Ad+) (N = 207), and children aged 36-59 months were randomised to MenACWY (N = 128) or Mencevax (N = 82). The toddlers then received a second vaccination at either 1, 6, or 12 months (6 groups total), while the children 36-59 months of age received a second vaccination at 6 or 12 months (4 groups total).

For subjects aged 36 to less than 60 months the primary objective was to compare the functional immune response 28 days after administration of one dose of MenACWY with that of a plain MenACWY PS vaccine, as measured by the percentage of subjects with human complement serum bactericidal activity (hSBA) ≥1:4 against *N meningitidis* serogroups A, C, W, and Y. Secondary objectives were to compare the functional immune response 28 days after administration of one dose of MenACWY with that of a MenACWY PS vaccine (Mencevax), as measured by hSBA GMTs and hSBA ≥1:8 against *N. meningitidis* serogroups A, C, W, and Y.

In addition, the following secondary objectives were to be evaluated using hSBA GMTs and percentage of responders with hSBA titers ≥1:4 and ≥1:8:

- The persistence of functional immune response at 6 or 12 months following administration of one dose of either MenACWY Ad- or MenACWY PS vaccine.
- The booster effect 21 days after one dose of MenACWY Ad- vaccine administered 6 or 12 months after the first dose of either MenACWY Ad- or MenACWY PS vaccine.

For subjects aged 12 to 35 months the following secondary objectives were to be evaluated using hSBA GMTs and percentage of responders with hSBA titers ≥1:4 and ≥1:8:

- The functional immune response 28 days after administration of one dose of either MenACWY Ad+ or MenACWY Ad-.
- The functional immune response 21 days after a second dose of either MenACWY Ad+ or MenACWY Ad- Ad- administered 1 month after the first dose.
- The persistence of functional immune response at 6 or 12 months following administration of one dose of either MenACWY Ad+ or MenACWY Ad-.
- The persistence of functional immune response at 12 months following administration of two doses of either MenACWY Ad+ or MenACWY Ad-.
- The booster effect 21 days after a second dose of either MenACWY Ad+ or MenACWY Ad- administered at 6 or 12 months after the first dose.

The primary results for children 3-5 years of age are presented in table 8. Secondary endpoints are presented in tables 8 and 9.

Table 8: Percentage of Subjects (95% CI) 36 to 59 Months Old with hSBA Titer ≥ 1:4 for A, C, W, and Y Serogroups

	1st Vaccination				2nd Vaccination 6 Months after 1st Vaccination[a]		2nd Vaccination 12 Months after 1st Vaccination[a]	
	Day 1 (Baseline)		Day 29 (28 Days after 1st Vacc.)		Day 169 (before 2nd)[c]	Day 190 (21 Days after 2nd)	Day 337 (before 2nd)[d]	Day 358 (21 Days after 2nd)
Serogroup	ACWY Ad- N=101	ACWY PS N=81	ACWY Ad- N=101	ACWY PS N=81	ACWY Ad- N=48	ACWY Ad- N=48	ACWY Ad- N=45	ACWY Ad- N=45
A	2% (0-7)	1% (0.032-7)	75% (66-83)	55% (43-66)	23% (12-37)	92% (80-98)	13% (5-27)	98% (88-100)
C	14% (8-23)	10% (4-19)	60% (49-69)	52% (40-63)	45% (30-60)	100% (92-100)	42% (28-58)	100% (92-100)
W	17% (10-26)	19% (11-29)	91% (84-96)	67% (55-77)	94% (82-99)	100% (92-100)	84% (71-94)	100% (92-100)
Y	10% (5-18)	11% (5-21)	77% (68-85)	67% (56-77)	70% (55-83)	100 (92-100)	80% (65-90)	100% (92-100)

[a] Subset of PP population receiving 2nd vaccine 6 months after 1st vaccination.
[b] Subset of PP population receiving 2nd vaccine 12 months after 1st vaccination.
[c] These values also show persistence 6 months after 1st vaccination.
[d] These values also show persistence 12 months after 1st vaccination.
Source : Table 14.2.1.1 and Table 14.2.1.3

The results using the hSBA titer ≥1:8 were similar to % with hSBA titer ≥ 1:4. The percentage of subjects with hSBA titers ≥ 1:8 was higher in the MenACWY Ad- group than in the MenACWY PS group for all serogroups (54% to 84% for MenACWY Ad-and 39% to 59% for MenACWY PS for the different serogroups). At 28 days after vaccination the GMTs increased in both groups, but elevations in GMT for serogroups A, W, and Y were more pronounced in the MenACWY Ad- group (GMR between 7.11 and 8.75 for MenACWY Ad- and 3.37 and 5.84 for MenACWY PS), whereas no relevant difference was observed for serogroup C.

Table 9: Percentage of Subjects (95% CI) 36 to 59 Months Old with hSBA Titer ≥ 1:8 for A, C, W, and Y Serogroups

	1st Vaccination				2nd Vaccination 6 Months after 1st Vaccination[a]		2nd Vaccination 12 Months after 1st Vaccination[b]	
	Day 1 (Baseline)		Day 29 (28 Days after 1st Vacc.)		Day 169 (before 2nd)[c]	Day 190 (21 Days after 2nd)	Day 337 (before 2nd)[d]	Day 358 (21 Days after 2nd)
Serogroup	ACWY Ad- N=101	ACWY PS N=81	ACWY Ad- N=101	ACWY PS N=81	ACWY Ad- N=48	ACWY Ad- N=48	ACWY Ad- N=45	ACWY Ad- N=45
A	2% (0-7)	0% (0-5)	61% (51-71)	39% (28-50)	10% (3-23)	90% (77-97)	9% (2-21)	98% (88-100)
C	5% (2-11)	8% (3-16)	54% (43-64)	39% (28-51)	32% (19-47)	96% (85-99)	24% (13-40)	100% (92-100)
W	15% (9-24)	14% (7-23)	84% (75-91)	59% (48-70)	77% (62-88)	100% (92-100)	76% (60-87)	100% (92-100)
Y	7% (3-14)	6% (2-14)	67% (57-76)	57% (45-68)	60% (44-74)	100% (92-100)	64% (49-78)	100% (92-100)

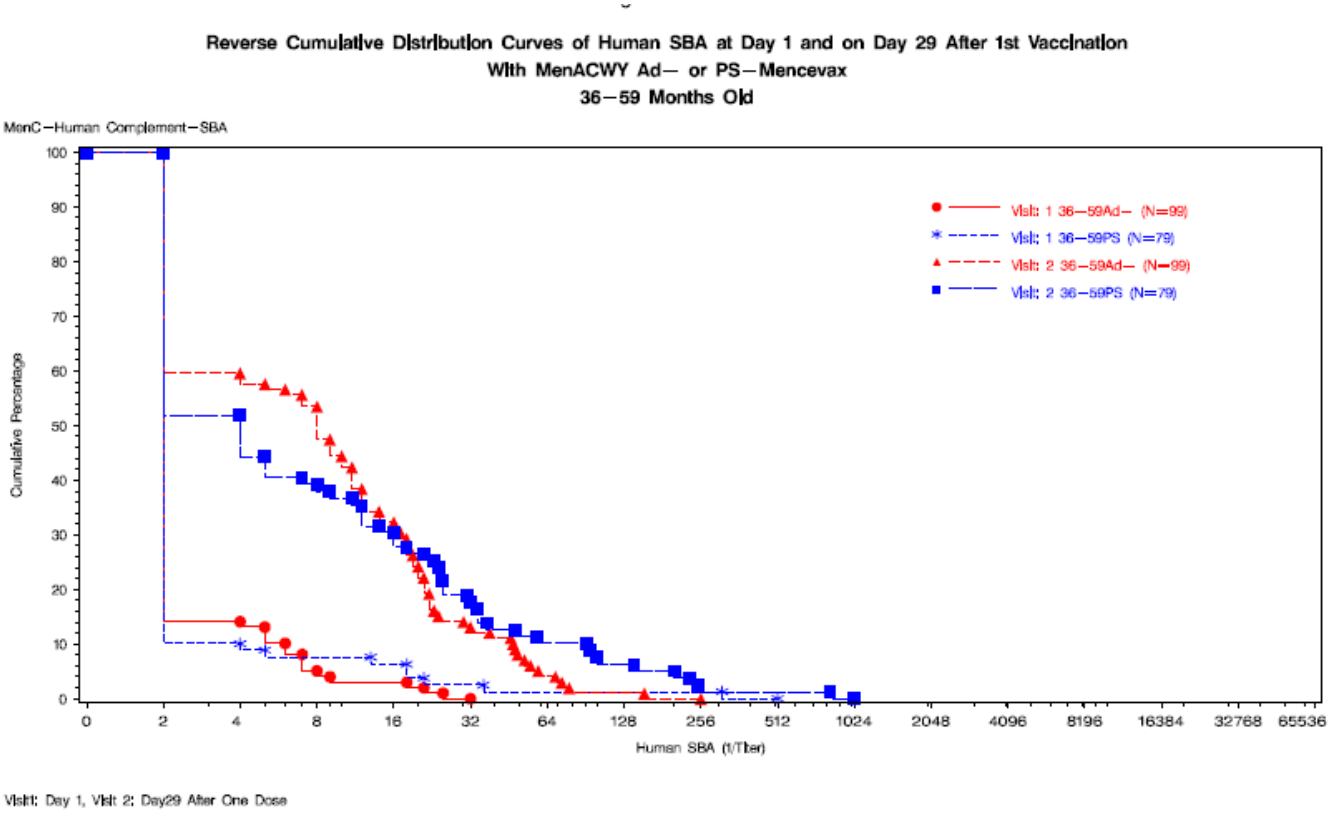
[a] Subset of PP population receiving 2nd vaccine 6 months after 1st vaccination.
[b] Subset of PP population receiving 2nd vaccine 12 months after 1st vaccination.
[c] These values also show persistence 6 months after 1st vaccination.
[d] These values also show persistence 12 months after 1st vaccination.
Source : Table 14.2.1.2 and Table 14.2.1.5

Table 10: GMTs and GMRs (95% CI) in Subjects 36 to 59 Months Old for A, C, W, and Y Serogroups

Variable/ Serogroup		1st Vaccination				2nd Vaccination 6 Months after 1st Vaccination[a]		2nd Vaccination 12 Months after 1st Vaccination[b]	
		Day 1 (Baseline)		Day 29 (28 Days after 1st Vacc.)		Day 169 (before 2nd)[c]	Day 190 (21 Days after 2nd)	Day 337 (before 2nd)[d]	Day 358 (21 Days after 2nd)
		ACWY Ad- N=101	ACWY PS N=81	ACWY Ad- N=101	ACWY PS N=81	ACWY Ad- N=48	ACWY Ad- N=48	ACWY Ad- N=45	ACWY Ad- N=45
GMT	A	2.06 (2.02-2.1)	2.03 (1.98-2.07)	15 (11-20)	6.82 (4.89-9.53)	2.84 (2.17-3.73)	51 (35-75)	2.51 (1.9-3.32)	149 (99-222)
	C	2.42 (2.22-2.65)	2.54 (2.3-2.8)	7.12 (5.45-9.3)	7.16 (5.31-9.65)	5.06 (3.43-7.46)	129 (83-200)	4.3 (2.89-6.39)	472 (301-739)
	W	3.05 (2.63-3.53)	3.14 (2.66-3.7)	24 (18-31)	12 (8.68-16)	22 (14-33)	371 (256-535)	20 (13-30)	1120 (769-1632)
	Y	2.42 (2.21-2.66)	2.46 (2.21-2.73)	21 (15-29)	14 (9.99-21)	11 (7.14-18)	247 (168-364)	18 (11-29)	911 (613-1353)
GMR	A	NA	NA	7.11 (5.28-9.57)	3.37 (2.41-4.7)	NA	18 (12-26)	NA	59 (40-87)
	C	NA	NA	2.94 (2.27-3.8)	2.82 (2.11-3.76)	NA	25 (17-38)	NA	110 (72-167)
	W	NA	NA	7.78 (5.87-10)	3.78 (2.77-5.18)	NA	17 (12-25)	NA	57 (39-84)
	Y	NA	NA	8.75 (6.38-12)	5.84 (4.09-8.34)	NA	22 (14-32)	NA	50 (33-76)

NA = not applicable
[a] Subset of PP population receiving 2nd vaccine 6 months after 1st vaccination.
[b] Subset of PP population receiving 2nd vaccine 12 months after 1st vaccination.
[c] These values also show persistence 6 months after 1st vaccination.
[d] These values also show persistence 12 months after 1st vaccination.
Source : Table 14.2.1.7 and Table 14.2.1.8

Figure 4: Reverse cumulative distribution curve of Human SBA at Day 1 and on Day 29 after 1st vaccination with MenACWY or PS-Mencevax (36-59 months old) for serogroug C



Persistence and Booster effect

The group of children aged 36 to 59 months was divided into two subgroups. One subgroup received a second vaccination (always MenACWY Ad-) at 6 months after the first vaccination with either MenACWY or MenACWY PS; the other subgroup received the second vaccination at 12 months after the first vaccination. Prior to the second vaccination, the hSBA titer was determined and GMT was calculated.

The functional immune response at 6 and 12 months after the first vaccination waned markedly for serogroup A, was maintained for serogroups W and Y, and was only moderately lower for serogroup C (see tables 9 and 10).

GMTs showed no remarkable differences between 6 and 12 months after vaccination: at 6 months after vaccination GMT for serogroup A was only slightly higher than baseline. For serogroup C GMT was slightly lower than at 28 days after vaccination (day 29: 7.91 and 6.31, respectively and 5.06 and 4.3 at 6 and 12 months after vaccination). GMRs for serogroup W showed no relevant changes over time, GMR for serogroup Y slightly decreased compared to day 29, but the decrease was similar at 6 and 12 months.

Independent of the time period between the first and second vaccination the percentage of subjects with an hSBA titer ≥1:4 was 100% for serogroups C, W, and Y at 21 days after the second vaccination. For serogroup A the percentages of subjects were 92% (second vaccination after 6 months) and 98% (second vaccination after 12 months). Similar results were obtained when using the hSBA titer ≥1:8. For all serogroups, GMT was about 3- to 4-fold higher in the subgroup of children who received the second vaccination 12 months after the first vaccination compared to children who received the second vaccination at 6 months.

Study V59P8

Study V59P8 is a phase 2, randomised, single-blind, controlled, single-center study to compare the safety and immunogenicity of One Dose of MenACWY with one dose of plain PS MenACWY vaccine (Menomune) in healthy children 2-10 years of age, in addition to an open-label study to assess the safety and immunogenicity of a single dose of MenACWY in healthy toddlers (12-23 months).

The primary objective was to compare the immunogenicity of a single dose of MenACWY with the immunogenicity of a single dose of licensed meningococcal ACWY polysaccharide vaccine (Menomune), defined as percentage of subjects with serum bactericidal activity (i.e., hSBA ≥ 1:4) directed against *N. meningitidis* serogroups A, C, W-135, and Y, at 1 month after vaccination, when administered to healthy children 2 to 10 years of age.

Secondary objectives included: Comparing the hSBA GMT's at 1 month following a single dose, comparing the immune response for 2-5 years old and 6-10 years old children separately, comparing persistence at the 12 months after a single dose of MenACWY in toddlers between 12 and 23 months of age with that of a PS MenACWY vaccine in children aged 3 to 5 years, and finally to compare the immunogenicity of a single dose of MenACWY and the immunogenicity of a single dose of licensed meningococcal ACWY polysaccharide vaccine (Menomune), defined as: percentage of subjects with serum bactericidal activity (i.e., hSBA ≥ 1:4) and hSBA GMT antibody response directed against *N. meningitidis* serogroups A, C, W-135, and Y at 12 months after vaccination, when administered to healthy children 2 to 10 years of age, overall and within the following age groups: 2 to 5 years of age and 6 to 10 years of age.

The primary response (% hSBA≥1:4) is presented in the following table:

Table 11: Primary Immunogenicity Variable: Percentage of Responders in Subjects Aged 2 to 10 Years (hSBA Titers ≥ 1:4) at One Month after Vaccination

Sero-group	Day	hSBA	Vaccine Group		Diff. MenACWY 2-10 – Menomune 2-10 95% CI (%)
			MenACWY 2-10	Menomune 2-10	
A	**1**	n (%) ≥ 1:4 95% CI (%) N	6 (2) 1 – 5 280	1 (0) 0.009 – 2 281	2 0 - 4
	29	n (%) ≥ 1:4 95% CI (%) N	228 (81) 76 – 86 280	125 (44) 39 – 51 281	37 **29 - 44**
C	**1**	n (%) ≥ 1:4 95% CI (%) N	80 (28) 23-34 281	81 (29) 23-34 283	0 -8 - 7
	29	n (%) ≥ 1:4 95% CI (%) N	232 (83) 78-87 281	181 (64) 58-70 283	19 **12 - 26**
W	**1**	n (%) ≥ 1:4 95% CI (%) N	111 (40) 34-46 279	108 (38) 33-44 282	1 -7 - 10
	29	n (%) ≥ 1:4 95% CI (%) N	263 (94) 91-97 279	202 (72) 66-77 282	23 **17 - 29**
Y	**1**	n (%) ≥ 1:4 95% CI (%) N	61 (22) 17-27 280	68 (24) 19-30 282	-2 -9 - 5
	29	n (%) ≥ 1:4 95% CI (%) N	254 (91) 87-94 280	167 (59) 53-65 282	31 **25 - 38**

Bold: 95% CI completely below or above 0%

Table 11b: Percentage of Responders in Subjects Aged 2 to 10 Years (hSBA Titers ≥ 1:8) at One and 12 Months after Vaccination

Sero-group	Day	Number (Percentage) of Responders n (%) hSBA ≥ 1:8 95% CI (%) N		Diff. MenACWY – Menomune 95% CI (%)
		Men ACWY	Meno-mune	hSBA titer ≥ 1:8
A	1	1 (0) 0.01 –2 253	1 (0) 0.011 – 2 238	0 -2 - 2
	29	203 (80) 75 – 85 253	89 (37) 31 – 44 238	43 **35 - 50**
	360	58 (23) 18 – 29 253	31 (13) 9 – 18 238	10 **3 - 17**
C	1	35 (14) 10 – 19 252	46 (19) 14 – 25 240	-5 -12 – 1
	29	185 (73) 68 – 79 252	133 (55) 49 – 62 240	18 **10 – 26**
	360	134 (53) 47 – 59 252	106 (44) 38 – 51 240	9 0 – 18
W	1	93 (37) 31 – 44 249	81 (34) 28 – 41 237	3 -5 - 12
	29	229 (92) 88 – 95 249	153 (65) 58 – 71 237	27 **21 - 34**
	360	225 (90) 86 – 94 249	106 (45) 38 – 51 237	46 **38 - 53**
Y	1	48 (19) 15 – 25 250	50 (21) 16 – 27 239	-2 -9 - 5
	29	220 (88) 83 – 92 250	132 (55) 49 – 62 239	33 **25 - 40**
	360	193 (77) 71 – 82 250	76 (32) 26 – 38 239	45 **37 - 53**

Both MenACWY and Menomune exhibited increased bactericidal activity at 1 month after vaccination (percentage of subjects with hSBA titers ≥ 1:4) relative to baseline for each serogroup, but the percentage of subjects with hSBA titers ≥ 1:4 was higher in the MenACWY group than in the Menomune group (81% to 94% for MenACWY and 44% to 72% for Menomune). The differences between MenACWY and Menomune groups were 37%, 19%, 23%, and 31% for the serogroups A, C, W, and Y, respectively. The lower limits of the 95% CIs for the differences at 1 month after vaccination were greater than 0% against all four serogroups, indicating statistical superiority of MenACWY over Menomune. Similarly, the differences in GMTs between the vaccine groups were statistically significant for all four serogroups ($P < 0.001$, see table 12). Results were similar when considering children aged 2-5 years and 6-10 years separately (exception, the response to serogroup C in 6-10 year olds which was similar for the two vaccines).

Table 12: Secondary Immunogenicity Variable: Geometric Mean hSBA Titers in Subjects Aged 2 to 10 Years at One Month After Vaccination

Sero-group	Day	hSBA	Vaccine Group		*P* value Group
			MenACWY 2-10	Menomune 2-10	
A	**1**	GMT 95% CI N	2.06 2.02-2.1 280	2.02 1.98-2.06 281	.16
	29	GMT 95% CI N	36 30-44 280	6.31 5.21-7.64 281	**< .001**
	29 / 1	GMR 95% CI N	18 15 – 21 280	3.13 2.59 – 3.7 281	**< .001**
C	**1**	GMT 95% CI N	3.07 2.77-3.4 281	3.33 3.01-3.68 283	.26
	29	GMT 95% CI N	26 21-34 281	15 12-20 283	**.002**
	29 / 1	GMR 95% CI N	8.61 6.98 – 11 281	4.63 3.76 – 5.71 283	**< .001**
W	**1**	GMT 95% CI N	5.74 4.86-6.78 279	5.63 4.77-6.65 282	.88
	29	GMT 95% CI N	60 50-71 279	14 12-17 282	**< .001**
	29 / 1	GMR 95% CI N	10 8.74-12 279	2.48 2.09-2.94 282	**<.001**
Y	**1**	GMT 95% CI N	3.32 2.95-3.73 280	3.34 2.97-3.76 282	.92
	29	GMT 95% CI N	54 44-66 280	11 9.29-14 282	**< .001**
	29 / 1	GMR 95% CI N	16 13-20 280	3.42 2.78-4.22 282	**<.001**

Persistence

Twelve months after vaccination, the number of responders (subjects with hSBA ≥ 1:4) decreased compared to 1-month data in both vaccine groups for all serogroups, and the number of responders was statistically significantly higher in the MenACWY group than in the Menomune group (the lower limit of all 95% CI for the difference between the two vaccine groups were greater than 0%). The decrease was most pronounced for serogroup A (from 82% to 28% responders at 1 and 12 months after MenACWY, and from 45% to 18% responders after vaccination with Menomune). Similar responder rates were observed at 1 and 12 months after vaccination for serogroups W and Y after MenACWY vaccination, but not after Menomune vaccination (for serogroup W, the responder rate decreased from 71% to 50% and for serogroup Y from 61% to 38%). The comparisons between MenACWY and Menomune always resulted in a lower limit of the 95% CIs that was greater than 0%, indicating superiority of MenACWY over Menomune. The corresponding GMT values showed a similar pattern, GMT values were higher after MenACWY than after Menomune at 12 months after vaccination (except for serogroup C)

Table 13: Percentage of Responders and Geometric Mean hSBA Titers in Children Aged 2 to 10 Years at 12 Months After Vaccination

Sero-group	Day	hSBA	Vaccine Group		Diff. (%) MenACWY – Menomune 95% CI (%)	hSBA	Vaccine Group		*P* Value Group
			Men ACWY 2-10	Meno-mune 2-10			Men ACWY 2-10	Meno-mune 2-10	
A	**360**	n (%) ≥ 1:4 95% CI (%) N	71 (28) 23 – 34 253	44 (18) 14 – 24 238	10 **2 - 17**	Day 360 GMT 95% CI N	3.88 3.39-4.44 253	3 2.61-3.44 238	**.009**
C	**360**	n (%) ≥ 1:4 95% CI (%) N	172 (68) 62 - 74 252	126 (53) 46 - 59 240	16 **7 - 24**	Day 360 GMT 95% CI N	11 8.64-13 252	9.02 7.23-11 240	**.27**
W	**360**	n (%) ≥ 1:4 95% CI (%) N	234 (94) 90 - 97 249	119 (50) 44 - 57 237	44 **37 – 51**	Day 360 GMT 95% CI N	42 35-50 249	7.57 6.33-9.07 237	**< .001**
Y	**360**	n (%) ≥ 1:4 95% CI (%) N	215 (86) 81 - 90 250	90 (38) 31 - 44 239	48 **41 – 56**	Day 360 GMT 95% CI N	27 22-33 250	5.29 4.34-6.45 239	**< .001**

Bold: 95% CI completely below or above 0% or *P* value < .05
Source: Tables 14.2.1.31 and 14.2.1.37

Study V59P10

Study V59P10 is a phase 3, randomised, observer-blind, controlled, multi-center study to compare the safety of one dose of MenACWY conjugate vaccine with that of a licensed MenACWY plain PS vaccine (Menomune) administered to healthy children 2-10 years of age. The primary objective was to compare the immunogenicity of a single injection of MenACWY conjugate vaccine with the immunogenicity of a single injection of Menomune, defined as the percentage of subjects with seroresponse in human serum bactericidal assay against *N meningitidis* serogroups A, C, W, and Y at 1 month after vaccination. Seroresponse was defined as in study V59P20.

In children 2-10 years of age, the percentages of subjects with seroresponse at one month post-vaccination was statistically superior in the MenACWY group than in the Menomune group for all four serogroups:

Table 14: Percentage (95%CI) of Subjects with Seroresponse by Baseline Titer, 1 Month Post-vaccination, Study V59P10, PP Population

		2-10 years		
Sero-group	Baseline Titer	MenACWY	Menomune	MenACWY-Menomune
A	< 1:4	N = 140 95 (90, 98)	N = 143 55 (46, 63)	40% (32, 49)
	≥ 1:4	N = 8 50 (16, 84)	N = 5 60 (15, 95)	-10% (-55, 41)
	Overall	N = 148 93 (87, 96)	N = 148 55 (46, 63)	38% (29, 41)
C	< 1:4	N = 109 85 (77, 91)	N = 100 60 (50, 70)	25% (14, 37)
	≥ 1:4	N = 38 71 (54, 85)	N = 44 34 (20, 50)	37% (16, 55)
	Overall	N = 147 82 (74, 88)	N = 144 52 (44, 60)	30% (19, 40)
W	< 1:4	N = 86 99 (94, 100)	N = 89 57 (46, 68)	42% (31, 52)
	≥ 1:4	N = 57 37 (24, 51)	N = 53 26 (15, 40)	10% (-7, 27)
	Overall	N = 143 74 (66, 81)	N = 142 46 (37, 54)	28% (17, 39)
Y	< 1:4	N = 121 87 (79, 92)	N = 124 62 (53, 71)	25% (14, 35)
	≥ 1:4	N = 25 56 (35, 76)	N = 22 68 (45, 86)	-12% (-38, 16)
	Overall	N = 146 82 (74, 87)	N = 146 63 (55, 71)	18% (8,28)

In children 2-10 years of age, GMTs at baseline were similar between the vaccine groups with no statistically significant differences for any serogroup. At one month post-vaccination, GMTs were statistically significantly higher in the MenACWY group than in the Menomune group for all four serogroups (A: 65 vs 11; vaccine group ratio of 5.86; 95% CI: [4.19, 8.19]) (C: 42 vs 20; vaccine group ratio of 2.08; 95% CI: [1.44, 3.01]) (W: 72 vs 20; vaccine group ratio of 3.58; 95% CI: [2.56, 5]) (Y: 47 vs 25; vaccine group ratio of 1.86; 95% CI: [1.24, 2.79])

Results for both age subgroups (2-5, 6-10 years) patterned similarly to the 2-10 years of age group, however for serogroups W and Y statistical superiority was not demonstrated in the 6-10 age group for all immunogenicity endpoints.

Persistence

In the overall population (2 to 10 years of age), the percentages of subjects with hSBA titer ≥ 1:8 at day 181 decreased compared with those observed at day 29 for all serogroups in both vaccine groups except serogroup Y in the MenACWY group

Table 15: Secondary Immunogenicity Objective: Percentage of Subjects with hSBA Titer ≥ 1:8 (95% CI) at Day 29 and Day 181 by Age Group, PP Population

		2-5 Years		6-10 Years	
Serogroup	**Study Day**	**MenACWY**	**Menomune**	**MenACWY**	**Menomune**
		N=70	**N=70**	**N=75**	**N=74**
A	**Day 29**	96% (88-99)	56% (43-68)	95% (87-99)	53% (41-64)
	Day 181	29% (18-41)	33% (22-45)	41% (30-53)	43% (32-55)
		N=68	**N=66**	**N=73**	**N=73**
C	**Day 29**	79% (68-88)	58% (45-70)	96% (88-99)	81% (70-89)
	Day 181	69% (57-80)	47% (35-60)	92% (83-97)	63% (51-74)
		N=66	**N=66**	**N=71**	**N=71**
W	**Day 29**	98% (92-100)	56% (43-68)	100% (95-100)	87% (77-94)
	Day 181	92% (83-97)	56% (43-68)	100% (95-100)	75% (63-84)
		N=67	**N=68**	**N=73**	**N=73**
Y	**Day 29**	82% (71-90)	50% (38-62)	95% (87-98)	84% (73-91)
	Day 181	85% (74-93)	49% (36-61)	93% (85-98)	68% (57-79)

Table 16: Secondary Immunogenicity Objective: Percentage of Subjects with hSBA Titer ≥ 1:8 (95% CI) at Day 29 and Day 181 by Age Group, PP Population

		2-10 Years		Vaccine Group Difference
Serogroup	**Study Day**	**MenACWY**	**Menomune**	**MenACWY 2-10 – Menomune 2-10 (95% CI)**
		N=145	**N=144**	
A	**Day 29**	95% (90-98)	54% (46-62)	41% (32, 50)
	Day 181	35% (27-44)	38% (30-47)	-3% (-14, 8)
		N=141	**N=139**	
C	**Day 29**	88% (81-93)	70% (61-77)	18% (9, 28)
	Day 181	81% (73-87)	55% (47-64)	25% (15, 36)**
		N=137	**N=137**	
W	**Day 29**	99% (96-100)	72% (64-80)	27% (20, 35)
	Day 181	96% (92-99)	66% (57-74)	31% (22, 39)**
		N=140	**N=141**	
Y	**Day 29**	89% (82-93)	67% (59-75)	21% (12, 31)
	Day 181	89% (83-94)	59% (50-67)	30% (21, 40)**

No clear age-dependent pattern was identified in the by age analysis of the percentages of subjects with hSBA titer ≥ 1:8 observed at day 181 vs. day 29. In the MenACWY group, for serogroups A, C, and W, a lower extent of decay was observed in the 6 to 10 compared to the 2 to 5 years age group. For serogroup Y in the MenACWY group, comparable percentages were seen for both age cohorts at

day 181 vs. day 29. As in the MenACWY group, in the Menomune group also, for serogroup A, lower extent of decay was observed in the older age group; conversely, for serogroups C, W, and Y in the Menomune group, a lower extent of decay was observed in the 2 to 5 years than in the 6 to 10 years age group. In both age cohorts, for serogroups C, W, and Y, the percentages of subjects with hSBA titer ≥1:8 at day 181 were consistently higher in the MenACWY than in the Menomune group. For serogroup A, the percentages were comparable in the MenACWY and Menomune groups although the decay was greater in the MenACWY group.

The results observed when a less conservative threshold, i.e., hSBA titer ≥ 1:4, was used, were generally similar to those observed in the analysis of the percentages of subjects with hSBA titer ≥1:8

In the overall population (2 to 10 years of age), the hSBA GMTs at day 181 decreased compared with those observed at day 29 for all serogroups in both vaccine groups (Table 17 below). In the MenACWY group, the extent of decay was lowest for serogroups W and Y and highest for serogroup A. For serogroups C, W, and Y, the hSBA GMTs at day 181 were consistently higher in the MenACWY than in the Menomune group (serogroup C: 22 vs. 11; serogroup W: 69 vs. 16; serogroup Y: 39 vs. 14), with p-values providing evidence of statistically significant difference between the two vaccines groups. The GMTs observed for serogroup A were similar between the two vaccine groups (5.06 vs. 5.85, respectively).

Table 17: Secondary Immunogenicity Objective: hSBA GMTs (95% CI) at Day 29 and Day 181 by Age Group - PP Population

		2 -5 Years		6 - 10 Years		2-10 Years		
Serogroup	**Day**	**MenACWY**	**Menomune**	**MenACWY**	**Menomune**	**MenACWY**	**Menomune**	**P-Value:**
		N=70	**N=70**	**N=75**	**N=74**	**N=145**	**N=144**	
A	Day 29	56 (40-79)	11 (7.46-15)	76 (55-106)	11 (7.62-15)	66 (52-83)	11 (8.33-13)	<.001
	Day 181	4.27 (3.10-5.88)	4.70 (3.41-6.46)	5.93 (4.35-8.07)	7.20 (5.28-9.83)	5.06 (4.05-6.33)	5.85 (4.68-7.32)	.37
		N=68	**N=66**	**N=73**	**N=73**	**N=141**	**N=139**	
C	Day 29	25 (17-36)	12 (8.12-18)	66 (46-95)	32 (23-47)	41 (31-54)	20 (15-27)	<.001
	Day 181	16 (12-23)	7.03 (5.00-9.88)	29 (21-40)	17 (12-24)	22 (17-28)	11 (8.84-14)	<.001
		N=66	**N=66**	**N=71**	**N=71**	**N=137**	**N=137**	
W	Day 29	60 (42-85)	12 (8.76-18)	90 (65-127)	34 (24-47)	74 (58-95)	21 (16-27)	<.001
	Day 181	58 (41-83)	12 (8.20-17)	82 (58-115)	22 (15-30)	69 (54-89)	16 (13-21)	<.001
		N=67	**N=68**	**N=73**	**N=73**	**N=140**	**N=141**	
Y	Day 29	33 (22-51)	14 (9.20-21)	65 (43-98)	47 (31-70)	47 (35-64)	26 (19-35)	.007
	Day 181	35 (24-53)	9.60 (6.47-14)	42 (28-61)	21 (14-31)	39 (29-51)	14 (11-19)	<.001

Source: Table 14.2.1.8, Table 14.2.1.9

2 doses vs 1 dose of MenACWY

Further to the CHMP request to provide further justification to support the recommendation of a single dose in children aged 2-5 years, as well as in the age group 6 to 10 years, the MAH provided an

overview of the data generated in the following three supportive clinical studies in which MenACWY was compared to a meningococcal polysaccharide (MPS) vaccine: V59P7, V59P8 and V59P10.

The point estimates of the seroresponse to each of the serogroups in each of the studies in a variety of population groups (European, US, Latin American) was always higher after MenACWY in comparison to the MPS vaccine, in most instances by a wide margin (Table 18).

Table 18: Seroresponse rate (hSBA) in phase II and early phase III studies in 2-5 years old subjects

Group	V59P7 (Fin/Pol)		V59P8 (US)		V59P10 (Argentina)	
	MenACWY	Mencevax (3-5 years)	MenACWY	Menomune	MenACWY	Menomune
A	N = 198 62 (55, 69)	N = 80 39 (28, 50)	N = 133 77 (69, 84)	N = 138 36 (28, 44)	N = 72 93 (85, 98)	N = 73 58 (45, 69)
C	N = 196 40 (33, 48)	N = 79 33 (23, 44)	N = 135 52 (43, 61)	N = 138 32 (24, 40)	N = 72 76 (65, 86)	N = 69 51 (38, 63)
W	N = 198 67 (60, 73)	N = 81 47 (36, 58)	N = 135 62 (53, 70)	N = 138 26 (19, 34)	N = 70 89 (79, 95)	N = 69 39 (28, 52)
Y	N = 196 63 (56, 70)	N = 79 52 (40, 63)	N = 134 72 (63, 79)	N = 138 33 (25, 41)	N = 71 79 (68, 88)	N = 71 49 (37, 61)

The MAH noted that, although the limitations of MPS vaccines are well documented (e.g., limited immunogenicity in ages < 2 years, lack of induction of immune memory, hyporesponsiveness with repeat dosing, etc.), there is good evidence that they are safe, well-tolerated and efficacious vaccines, including in children aged 2 to 10 years. The measured vaccine efficacy in the literature of MPS vaccines supported the conclusion that a single dose is a reasonable dosing regimen for this age group, both with data derived from the Meningitis belt in Africa and in other settings.

The MAH provided data from a subset of sera tested using the rabbit SBA from children aged 2-10 years from study V59P20. The results of these analyses showed that the percentage of subjects achieving a four-fold rise in rSBA against all 4 serogroups ranged from 93-99% for 2 to 5 year olds and 93- 96% for 6 to 10 year olds (table 19).

Table 19: Percentage (95% CI) of subjects with seroresponse (95% CI) at 28 days after vaccination, by age group (V59P20, rSBA)

	Ages 2-5 years			Ages 6-10 years		
Serogroup	MenACWY	Menactra	(MenACWY-Menactra)	MenACWY	Menactra	(MenACWY-Menactra)
A	93% (86-97) N=99	95% (89-98) N=100	-2% (-9.5 – 5.0)*	94% (87-97) N=108	88% (80-93) N=106	6% (-2.1 – 14.2)*
C	96% (90-99) N=98	88% (80-94) N=100	8% (0.4 – 16.2)**	93% (86-97) N=108	79% (70-87) N=106	13% (4.3 – 22.9)**
W	99% (94-100) N=98	94% (87-98) N=100	5% (-0.2 – 11.5)*	95% (90-98) N=108	93% (87-97) N=106	2% (-4.6 – 8.9)*
Y	99% (94-100) N=97	93% (86-97) N=100	6% (0.6 – 12.8)**	96% (91-99) N=108	94% (88-98) N=106	2% (-4.2 – 8.5)*

Persistence of bactericidal antibodies

The MAH provided a comparison of the decline in antibody titres between MenACWY and MPS across studies. The percentage of subjects with hSBA ≥ 1:8 or achieving a seroresponse 1 month after vaccination is higher in those vaccinated with MenACWY than in those vaccinated with a meningococcal polysaccharide vaccine (MPS) across different MAH studies across all serogroups. At 6 or 12 months after vaccination, the point estimates of the percentages of subjects that maintained an hSBA ≥ 1:8 were also higher for all serogroups in both studies except for serogroup A in study V59P10 where the results were similar at the 6 month post-vaccination time point (Table 20). Although the 1 month post-vaccination time point has a higher percentage of subjects with an hSBA ≥ 1:8 for serogroup C in the US study (V59P8) after MenACWY (73% (95% CI 68-79%)) than after MenPS (55% (95% CI 49-62%)), the relative decline appears larger at 1 years post vaccination in the MenACWY group (53% (47-59%) vs. 44% (38-51%) after MenACWY vs. MenPS, respectively). This was not observed in the similar study conducted in Argentina (V59P10) where the opposite was observed: the percentage of subject with hSBA ≥ 1:8 in the MenACWY group dropped by 7% (from 88% to 81%) and the MPS group dropped by 15% (from 70% to 55%) during the follow-up period.

In study V59P6E1, 76% (95% CI 62-87%) of adolescents vaccinated five years previously with MenACWY maintained an hSBA ≥ 1:8 (versus 62% (95% CI 47-75%) of MenPS recipients). This represents a rather flat curve over time as among those same subjects vaccinated with MenACWY originally, 84% (95% CI 71-93%) had an hSBA ≥ 1:8 at one month post-vaccination.

Table 20: Percentage (95%CI) of subjects with hSBA ≥ 1:8, 6 or 12 months post-vaccination, 2-10 years of age, studies V59P8 and V59P10, PP population

		V59P8			V59P10		
Sero-group	**Timepoint**	**MenACWY**	**Menomune**	**ACWY-Menomune**	**MenACWY**	**Menomune**	**ACWY-Menomune**
A		N = 253	N = 238		N = 145	N = 144	
	1 month	80 (75, 85)	37 (31, 44)	43 (35, 50)	95 (90, 98)	54 (46, 62)	41 (32, 50)
	6 months	NA	NA	NA	35 (27, 44)	38 (30, 47)	-3 (-14, 8)
	12 months	23 (18, 29)	13 (9, 18)	10 (3, 17)	NA	NA	NA
C		N = 252	N = 240		N = 141	N = 139	
	1 month	73 (68, 79)	55 (49, 62)	18 (10, 26)	88 (81, 93)	70 (61, 77)	18 (9, 28)
	6 months	NA	NA	NA	81 (73, 87)	55 (47, 64)	25 (15, 36)
	12 months	53 (47, 59)	44 (38, 51)	9 (0, 18)	NA	NA	NA
W		N = 249	N = 237		N = 137	N = 137	
	1 month	92 (88, 95)	65 (58, 71)	27 (21, 34)	99 (96, 100)	72 (64, 80)	27 (20, 35)
	6 months	NA	NA	NA	96 (92, 99)	66 (57, 74)	31 (22, 39)
	12 months	90 (86, 94)	45 (38, 51)	46 (38, 53)	NA	NA	NA
Y		N = 250	N = 239		N = 140	N = 141	
	1 month	88 (83, 92)	55 (49, 62)	33 (25, 40)	89 (82, 93)	67 (59, 75)	21 (12, 31)
	6 months	NA	NA	NA	89 (83, 94)	59 (50, 67)	30 (21, 40)
	12 months	77 (71-82)	32 (26-38)	45 (37, 53)	NA	NA	

Regarding serogroup A, a poor persistence of hSBA titers for serogroup A after vaccination is observed where evaluated in both study V59P8 (hSBA ≥ 1:8 of 23% (95% CI 18-29%) at 1 year post-vaccination) and in study V59P10 (hSBA ≥ 1:8 of 35% (95% CI 27-44%) at 6 months post-

vaccination). These trends are similar to those observed in other age groups for serogroup A when using the hSBA including infants prior to the 12 month booster vaccination and in adolescents after a single dose of meningococcal vaccine. Based on the hSBA results in adults and adolescents (study V59P13E1), the antibodies against MenA have decreased significantly at 21 months post primary series, with only 37% with hSBA ≥ 1:8. At 21 months 38% (32-44%, N=275) have a hSBA ≥ 1:4.

Although no persistence data with rSBA has been generated in the 2 to 10 year old age group, the MAH presented results from adolescents. The percentage of subjects with an rSBA ≥ 1:8 against serogroup A was 96% at 5 years after vaccination, rSBA GMTs also remained very high at 952 among the per protocol population (n=48).

Observed variability in immune response across studies

The MAH provided an analysis of the observed variability in immune responses (Table 21) to vaccination after MenACWY across studies in different populations/regions and age groups. The following aspects were considered: intrinsic host (e.g., genetic-, age-related) differences, environmental (e.g., priming-, exposure-related) differences or assay-related differences.

Table 21: Ranges of GMTs (hSBA) across different age groups in MenACWY program

Serogroup	12 months old	2-5 years old	6-10 years old	11-18 years old
A	11 - 17	14 - 54	35-77	29 - 67
C	23 - 40	14 - 26	36-64	58 - 87
W	11- 30	12 - 43	61-87	49 - 159
Y	7.5 - 10	17 - 42	34- 64	51 - 100

Intrinsic (host) factors

Differences across age groups in immune responses are not unexpected, as maturing immune systems and/or age-dependent exposures to immunologic priming events are well described and seen above in Table 21. These underlying differences are the rationale for varied dosing regimens required in the different age groups. Within the MenACWY program, there were moderate differences in mean age at vaccination which may also contribute to some of the differences within each age strata. In particular, in study V59P7 where there has been increased attention to the overall lower response rates across all vaccine groups, the mean age of MenACWY recipients was 2.7 years versus a range of 3.3 – 3.6 years in MenACWY recipients in studies V59P8, V59P10 and V59P20. Since age-related improvements in immune responses are marked in this age range, this may be a significant factor that contributes to differences between studies.

Environmental factors

Geographic differences in the immune responses to certain vaccines is not a new observation and has been reported after polio, Hib as well as pneumococcal vaccination. There are a number of possible explanations as to the differences in vaccine responses. Some environmental factors such as previous vaccination with DTPw- versus DTPa combination vaccines or pneumococcal conjugate vaccines may play a role. It is difficult though in the case of MenACWY to reconcile that 2-5 year olds in the highest responder country (Argentina) and the lowest responder country (Finland) were both recipients of DTPw-containing priming vaccines. More likely the differences are related to other colonies/infecting bacteria in the local environment. The timing and the colonization with different types of Neisseria species is associated with certain age groups. These have been studied in a limited set of geographies

so differences might exist in this pattern across countries. In infants up to 2 years of age colonization with *N. lactamica* is significant while in adolescents there is a transition to higher rates of carriage with *N. meningitidis*. Antibodies that are cross-reactive against meningococci are present in infants after carriage of *N. lactamica*. Colonization of infants starts with the waning of maternal antibodies and continues in the early childhood (Gold R. et al, 1978; Bennett JS et al., 2005). Thus, differences in pre-titers in older age groups (i.e., maternal antibodies) may translate into a different dynamic of carriage during early infancy and thus affect subsequent responses to meningococcal vaccination.

MenACWY experience with intrinsic and environmental factors

It is difficult to separate out intrinsic factors from environmental factors due to genetic differences since both can be related to the countries or regions in which the studies are conducted. In several age groups in the MenACWY program there were at least two studies conducted in the same region, it is thus possible to examine the cumulative effects of these factors by comparing across studies. For MenACWY responses, when studying the same age groups within the same regions/countries, this variability was greatly decreased as seen in Table 22. In each of the study pairings shown in Table 22, one study was conducted during phase 2 and the other during phase 3 and all were conducted in North America. Studies were conducted (and assays run) between 2 and 4 years apart for each comparison; nonetheless, the percentage of subjects with an hSBA ≥ 1:8 was quite similar between the groups.

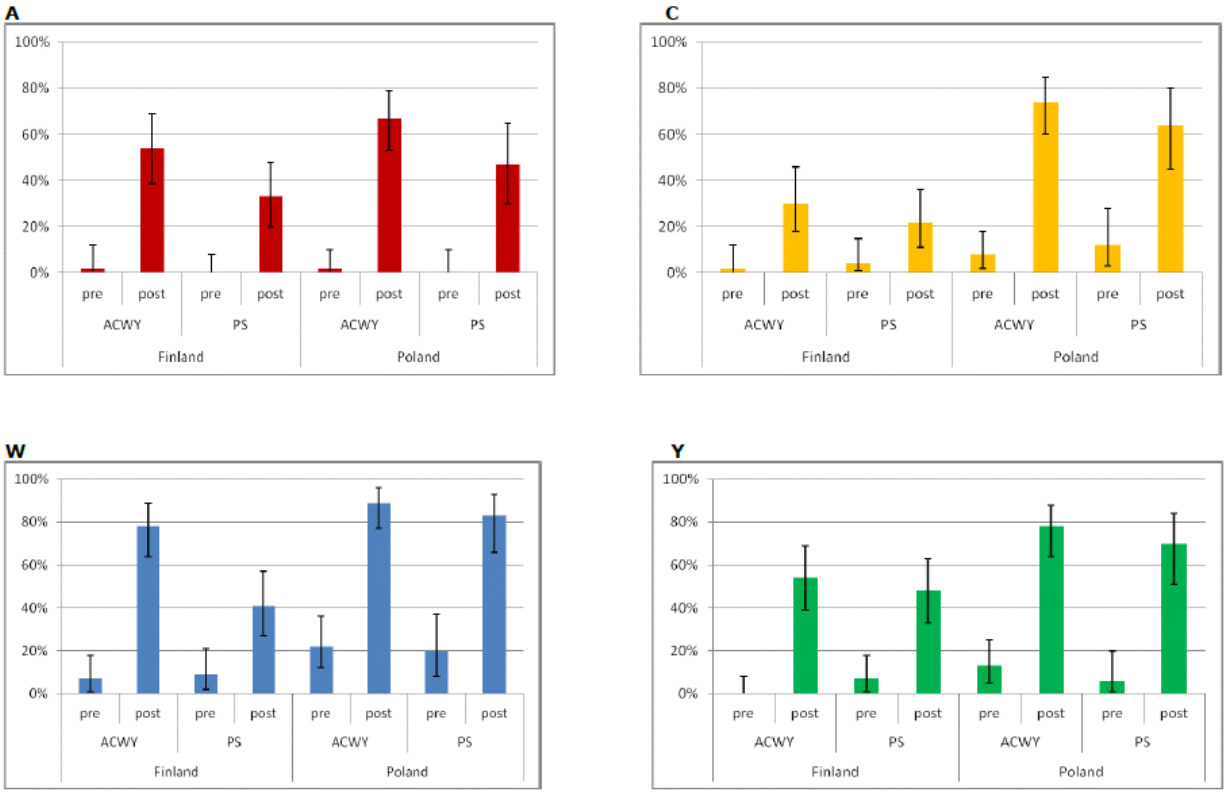
Table 22: Within US/Canada analyses, percentage of subjects with hSBA ≥ 1:8 by age group, PP population

		Single Dose, Toddlers (1 to 2 years)		Single Dose, Children (2 to 10 years)		Single Dose, Adolescents (11 to 18 years)	
Sero-group		V59P8 (US)	V59P14 (US subset)	V59P8 (US)	V59P20 (US/CA)	V59P6 (US)	V59P13 (US)
A	hSBA ≥ 1:8	75	72	79	75	81	75
	95% CI	(69, 81)	(60, 81)	(74, 84)	(72, 77)	(74, 87)	(73, 78)
	N	N = 240	N = 74	N = 280	N = 1157	N = 148	N = 1075
C	hSBA ≥ 1:8	87	90	73	72	83	84
	95% CI	(82, 91)	(81, 96)	(68, 78)	(70, 75)	(76, 89)	(82, 86)
	N	N = 241	N = 73	N = 281	N = 1161	N = 148	N = 1483
W	hSBA ≥ 1:8	77	58	92	90	90	96
	95% CI	(71, 82)	(45, 69)	(88, 95)	(88, 92)	(84, 95)	(95, 97)
	N	N = 240	N = 73	N = 279	N = 1136	N = 147	N = 1024
Y	hSBA ≥ 1:8	51	56	88	77	95	88
	95% CI	(45, 58)	(43, 68)	(83, 91)	(75, 80)	(90, 98)	(85, 90)
	N	N = 238	N = 68	N = 280	N = 1138	N = 147	N = 1036

A more prominent example from the MAH MenACWY program where between country differences were observed was in study V59P7. This study was conducted in both Finland and Poland with a slight majority of subjects enrolled in Finland. All serologic testing was performed simultaneously in the same lab for the same study visits. Obvious differences in vaccine responses between subjects from Finland and Poland were observed (Figure 5). The subjects from Finland had both lower pre- and post-vaccination hSBA titers compared to subjects from Poland. In particular, the difference between Finnish and Polish children was most obvious in the percentage of children aged 36-59 months with hSBA ≥ 1:8 after MenACWY against serogroup C, where Finnish children went from 2% (95% CI 0-12%) to 30% (95% CI 18-46%) whereas Polish children went from 8% (95% CI 2-18%) to 74% (95% CI 60-85%). The pattern was the same for the MPS comparator group with higher responses in Poland than in Finland (although in both countries, responses to MenACWY were higher than MPS). There were

similar observations for serogroups W and Y with higher responses in Polish versus Finnish subjects, although the confidence intervals were overlapping for some of the comparisons.

Figure 5: Study V59P7, percentage of subjects with hSBA ≥ 1:8 by country (Finland/Poland) among subjects aged 36-59 months



hSBA assay

All studies included in the submissions were tested with the MenACWY-hSBA in Germany with no changes introduced since its validation in 2005. Although meticulous efforts were maintained to minimize any between study differences, by necessity for each study certain test conditions were different. These may include different complement- and media-lots, number of technicians testing per study, speed of testing, etc. In order to monitor and control the performance of the assay over time, for each serogroup tested a set of 3 control sera is included in the assay: a high, low and negative control sera. The results of both the high and low control sera must fall within a pre-specified range and the negative control must have a titer of < 4. For each high and low control sera, control charts are maintained over time to detect shifts or drifts in the assay over time.

Within each serogroup the results seen for control sera were within the expected variability of the assay. As control sera is of limited volume, on occasion a change in the control sera is necessary so that all studies could not be tested using the same set of controls. An evaluation of the assay controls for the MenACWY-hSBA was conducted retrospectively for the time period 2005 to 2009 and for the year 2010. Slight differences in the performance of the assay could be detected through continuous monitoring of the control sera. However, differences seen between studies were within the expected variability of the serum bactericidal assay. Over time, the values for the control sera did vary in both directions and were not indicative of a general trend toward either higher or lower values within or across studies. Thus, although theoretical differences in assay characteristics cannot be ruled out, the

controls included in each assay which are present across studies are critical to minimizing any meaningful inter-study differences.

Discussion on clinical efficacy

Design and conduct of clinical studies

In the CHMP scientific advice pertaining to the submission the MAH was urged to include a comparative study with a monovalent conjugated MenC vaccine, as this was considered the most relevant comparator available in the EU. Polysaccharide vaccines are licensed in some countries for children from 2 years of age, and therefore for serogroups A, W, Y these are considered relevant as comparators. For MenC, the conjugated MenC vaccine is the more relevant comparator. The MAH has chosen to design a comparative study with Menactra, a diphtheria toxoid conjugated MenACWY vaccine (V59P20). This forms the pivotal trial for this present variation application. Since Menactra is not licensed in the EU, the comparison is informative but holds little direct relevance. Nonetheless, studies V59P7, V59P8 and V59P10 provide additional insight in the comparative immunogenicity versus polysaccharide vaccines and, which is considered just as important, insight in the persistence of bactericidal antibodies and the boosterability of MenACWY in this age group.

The indication proposed for this age group is only those who are at increased risk of exposure. The epidemiology of meningococcal infection and the MenC vaccination programmes across different EU countries (all in children <2 years) result to no or little risk of disease due to MenA, C, W, Y for this age group, although noted that MenY is on the increase in some countries. As such, this vaccine is likely to be reserved for children travelling to areas where they would be at risk of exposure to MenA, W or Y or possibly to be used in case of an outbreak. As such it is agreed with the MAH that a head-to-head comparison with a monovalent conjugated MenC vaccine is less relevant for the current indication.

Efficacy data and additional analyses

- MenACWY versus Menactra

The overall response to MenACWY in study V59P20 was moderate: in children aged 2 to 5 years, the percentage of seroresponders at 1 month postvaccination was 72%, 60%, 72% and 66% for serogroups A, C, W and Y respectively. In children aged 6 to 10 years, the percentage of seroresponders was 77%, 63%, 57% and 58% for serogroups A, C, W and Y respectively. The low response appears mostly driven by a low response in those with baseline hSBA≥1:4, in which the response is clearly less than in those without baseline antibodies (especially for serogroups W and Y). This was also observed in the studies in children, adolescents and adults aged 11 and older submitted at the time of the initial MAA. The MAH demonstrated at the time that there was no evidence of hyporesponsiveness, which is the main concern with such an observation. There is momentarily sufficient evidence demonstrating the boosterability of MenACWY therefore hyporesponsiveness is of no concern. Importantly, for serogroups A, C, W and Y respectively 75%, 72%, 90% and 77% of children aged 2-10 years achieve hSBA≥1:8 following vaccination regardless of baseline titres.

- MenACWY versus Polysaccharide vaccine

Study V59P7 provides relevant insight in the comparison with a plain polysaccharide tetravalent vaccine. Overall, as expected, the response is higher with MenACWY as compared to the response to a plain PS MenACWY vaccine. However, the GMT for serogroup C are very similar, and the point estimate is numerically higher for the PS vaccine (which is not in line with the %hSBA ≥1:4, 1:8).

Unlike study V59P7, statistical superiority of MenACWY over a plain polysaccharide tetravalent vaccine (Menomune) was demonstrated in study V59P8. The response to MenC is also somewhat higher in this study than what was seen in study V59P7, and the GMTs are higher in the MenACWY group than the Menomune group.

In relation to study V59P10, the CHMP had indicated in a scientific advice that a non-inferiority approach in this study was not supported. In line with the experience with conjugated MenC vaccines in the EU the MAH was expected to demonstrate superiority to meningococcal PS vaccines. Although superiority was not demonstrated for each immunogenicity endpoint for serogroups W and Y, overall the response to MenACWY appears higher than the response to Menomune.

- 2 doses versus 1 dose of MenACWY

The available data points out that the hSBA response following one dose in children aged 2-6 years can be increased with a second dose. Nonetheless, the MAH correctly point out that this response following one dose is clearly at least as good as the response following plain polysaccharide vaccines, to which MenACWY was compared. As the benefit of one dose with these vaccines has been shown, one dose of Menveo in this age group can also be considered adequate, especially considering the added benefit of the conjugated vaccine eliciting a T-cell dependent response. It should be noted however that the main reason for limiting the dosage of plain polysaccharide vaccines to one dose only was to avoid hyporesponsiveness and not necessarily that the response after one dose was optimal.

The MAH mentions that the hSBA is conservative and that it may underestimate vaccine efficacy, the validity of these arguments are difficult to assess. While it may be agreed that hSBA generally gives a conservative estimate for protection it is impossible to quantify how and whether this is in all epidemiological situations, for all serogroups, for all age groups etc. There is no clear evidence to indicate that the rSBA data are more predictive of vaccine efficacy than the hSBA, and it is becoming increasingly clear that there is no good correlation between the two assays for all serogroups under all circumstances. This was also found in a study sponsored by the MAH (Gill et al, 2011, Vaccine 30; 29–34) where correlations between hSBA and rSBA were weak for serogroups A, W-135 and Y (Pearsson correlation: range −0.15 to 0.57), and better for serogroup C (0.46 to 0.78).

Nonetheless, there are clear indications of an additional benefit of a second dose in children aged 2 to 5 years that possibly outweigh the additional risks associated with a second dose. The MAH is planning a study (Study V59_57) to compare one versus two doses in children aged 2 to 10 years. The study shall provide additional information about the safety and immunogenicity and persistence of bactericidal antibodies following two doses as compared to one dose. These results are needed to determine the added benefits of a second dose versus the increased risks. The MAH will submit the results of this study as soon as they are available.

- Persistence data

Persistence of bactericidal antibodies against serogroup A in study V59P7 is extremely poor as seen in previous studies in children >11 years and adults. For serogroup C a marked decrease in bactericidal antibodies after already 6 months is also observed. Although a good booster response is seen, the actual presence of bactericidal antibodies is considered more important for protection against invasive disease.

In study V59P8, problems with persistence of antibodies against serogroup A are also observed, and to a lesser degree with MenC. Of note, persistence of bactericidal antibodies is improved with the conjugated MenACWY vaccine compared to the plain PS vaccine, except for MenC where the decrease of bactericidal antibodies might be larger than in the Menomune group. As regards to persistence data from study V59P10, the response rate for MenACWY was remarkably higher in this study than what

was seen in V59P20, but also phase II studies V59P7 and V59P8. The observation of the relative larger decline in bactericidal Abs for serogroup C in the MenACWY arm as compared to the PS arm in V59P8 is not observed in study V59P10, where a comparison with the same PS vaccine was made albeit over a shorter period (6 months rather than 12 months).

In 2 to 10 years old, there currently is no long-term follow-up (> 1 year) and all data has been generated using the hSBA. The MAH has plans to follow-up the subjects from the larger phase 3 study V59P20 at a five year time point and this data will be available in 2013 from the extension study, V59P20E1. The data from study V59P20E1 will be important to determine whether immunogenicity can be maintained for all serogroups over time and to help determine when the optimal timing of a booster dose would be.

The decline in antibodies against serogroups A is of particular concern. Considering the data presented so far, not only for children aged 2-10 years but also adolescents/adults, it appears that a booster dose is needed to maintain bactericidal Ab for serogroup A when relying on the hSBA data. However, this is not confirmed by the rSBA results in adolescents, where concerns exist on the reliability of the results for MenA. Considering the importance of this serogroup for travellers, it should be advised that children who are at (renewed) risk of exposure should receive a booster dose. If the timing were based upon the hSBA results from study V59P10, it would be after 6 months, as in study V59P10 31% of children aged 2-5 years and 45% of children aged 6-10 years had hSBA ≥ 1:4 six months following vaccination. However to determine the appropriate timing the value of the hSBA relative to the rSBA results for MenA (persistence) data should be clarified. In the meantime, a warning has been included in section 4.4 of the SmPC that there is a steep decline in antibodies and as such a booster dose should be considered for persons who remain at risk of exposure to MenA. In section 4.2, a cross reference to sections 4.4 and 5.1 has also been added following the statement "The need for, and timing of, a booster dose of Menveo has not yet been determined." In addition, the MAH is recommended to make a recommendation on the need and timing for a booster dose once relevant data are available. The MAH is reminded of its responsibility to update the product information in accordance with Article 16 of Regulation (EC) No 726/2004.

- Variability in immune response across studies

The MAH has provided a detailed discussion of possible explanations for the observed variability. The use of a central laboratory and of control sera in the assay rule out that the variation observed is due to variation in the assay. Furthermore, the presentation (vial/vial versus vial/syringe) was found not to be contributing significantly to the observed variation. The MAH also clarified that in phase II studies mostly the vial/vial presentation was used and the vial/syringe presentation was used in phase III study V59P20. Other factors as discussed by the MAH could possibly provide an explanation, however it is agreed that it is difficult to single out what is causing the variation, as it also could be a combination of factors. It is important to keep in mind that if the rSBA were used responses would likely be higher, as this is inherent to the rSBA. The hSBA is more discriminative in this respect. Data from study V59P7 are considered important information for the healthcare provider since they reflect the performance of Menveo under a certain set of circumstances, and thus have been included in section 5.1 of the SmPC.

- Concomitant administration

No data on Co-administration of MenACWY with other vaccines has been provided for the 2-10 year age group. Co-administration of MenACWY with travellers vaccines (Japanese encephalitis, Typhoid, Yellow fever, HepA, HepB and Rabies) is currently being evaluated in two studies in adults. The MAH will provide results of these studies in a timely manner after completion.

Conclusions on clinical efficacy

Two phase II studies and two phase III studies were submitted in context of this type II variation application. All studies were in children aged 2-10 years, except V59P7 where the subjects were 2-5 years old, and took place in different countries across the world. Comparisons were made with licensed plain polysaccharide MenACWY vaccines (Mencevax, Menomune) licensed in the EU and with a diphtheria toxoid conjugated MenACWY vaccine (Menactra) licensed outside the EU only. The different studies provided data following a single dose and limited data following two doses (in the age group 2-5 years).

As the immune responses after a single dose of MenACWY is generally higher than following the licensed comparator polysaccharide vaccines in different studies, and as MenACWY induces a T-cell dependent immune response, although with some increased reactogenicity as compared to comparator vaccines, the overall Benefit Risk of one dose of MenACWY in children aged 2-10 years who are at increased risk of exposure to serogroup A, C, W-135 or Y is positive.

Data is available on persistence of antibodies up to 12 months and booster response after 6 and 12 months. Across all studies that measure persistence, persistence for serogroup A is poor.

Clinical safety

Patient exposure

The integrated summary of clinical safety in children aged 2 to 10 years includes clinical data for 3181 children from three phase II studies, V59P7, V59P8, and V59P10, and one phase III study (V59P20). The safety populations in each study are presented in table 23.

Table 23: MenACWY Studies in Subject Aged 2 to 10 Years: Number of Subjects Exposed to at Least One Injection of Meningococcal Vaccination

		Single Meningococcal Vaccination			Two Doses of Meningococcal Vaccination (ages 2 to 5 years only)		Total MenACWY[c]
	Study	MenACWY	Menactra	Menomune	MenACWY→ MenACWY[a]	Mencevax→ MenACWY[b]	
2-5 years	V59P7	--	--	--	224	74	298
	V59P8	151	--	153	--	--	151
	V59P10	451	--	265	--	--	451
	V59P20	693	684	--	351	--	1044
	Total	**1295**	**684**	**418**	**575**	**74**	**1944**
6-10 years	V59P8	157	--	157	--	--	157
	V59P10	498	--	286	--	--	498
	V59P20	582	571	--	--	--	582
	Total	**1237**	**571**	**443**	--	--	**1237**
2-10 years	V59P7	--	--	--	224	74	298
	V59P8	308	--	310	--	--	308
	V59P10	949	--	551	--	--	949
	V59P20	1275	1255	--	351	--	1626
	Total	**2532**	**1255**	**861**	**575**	**74**	**3181**

Adverse events

Solicited Adverse Events

An overview of reactogenicity is presented in Table 24.

Table 24: Overview of Reactogenicity: Percentages of Children Reporting Solicited AEs (Local and Systemic Reactions), by Age, by Vaccination, Pooled Analysis

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

	2nd Vaccination (2-5 years)	
	MenACWY→MenACWY[d] N=550	Mencevax→MenACWY[e] N=74
Any Reaction	49%	43%
Any Local Reaction	37%	35%
Any Systemic Reaction	27%	14%

Source: module 5, section 5.3.5.3, ISS Tables, Table 6, Table 6.1, Table 6.2, Table 7.1, Table 7.2, and Table 8
[a]MenACWY: studies V59P7, V59P8, V59P10, and V59P20, Menactra: study V59P20; Menomune: studies V59P8 and V59P10; Mencevax: study V59P7 (only 3-5 years age group);
[b]MenACWY: studies V59P8, V59P10, and V59P20; Menactra: study V59P20; Menomune: studies V59P8 and V59P10;
[c]MenACWY: studies V59P7 (only 2-5 years age group, the comparator, Mencevax, administered only in the 3-5 years age group, is presented in the 2-5 years fields of this table), V59P8, V59P10, and V59P20; Menactra: V59P20, Menomune: studies V59P8 and V59P10;
[d]Studies V59P7 and V59P20;
[e]Study V59P7.

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

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

Local reactogenicity

The pooled analysis of solicited local reactions after the first/single meningococcal vaccination in the overall 2 to 10 years age group was performed in 3107 MenACWY subjects (studies V59P7, V59P8, V59P10, and V59P20), 1255 Menactra subjects (study V59P20), and 861 Menomune subjects (studies V59P8 and V59P10).

During the 7-day reporting period following the first/single meningococcal vaccination, in the overall 2 to 10 years age population, pain was the most commonly reported local reaction. Pain of any severity was reported by similar percentages after MenACWY and Menomune (31% and 28%, respectively), while the reporting rates observed for Menactra were higher (40%). Reports of severe

pain were similar and low in all vaccine groups (range, <1% to 1%). Erythema and induration (any and severe [i.e., > 50mm]) were reported by similar percentages after MenACWY and Menactra and by considerably lower percentages after Menomune.

Table 25: Percentages of Children Ages 2 to 10 Reporting Any and (Severe) Local Reactions after First/Single Meningococcal Vaccination, Days 1 to 7 and 1 to 3, Pooled Analysis

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

Source: module 5, section 5.3.5.3, ISS Tables, Table 12 and Table 15;
[a]Tenderness in study V59P7; pain/tenderness were graded as none, mild (defined as "minor light reaction to touch"), moderate (defined as "cried or protested to touch"), or severe (defined as "cried when injected limb was moved").

Across the vaccine groups, in the majority of subjects, local solicited reactions (any and severe) occurred within the first 3 days postvaccination: no more than a 1% difference in the percentages reporting local reactions of any severity was observed for days 1 to 7 vs. days 1 to 3; the respective percentages for severe local reactions were the same for days 1 to 7 and 1 to 3. Overall, the majority of local reactions reported following the first/single vaccination with MenACWY were mild to moderate in severity and transient in duration.

Systemic reactogenicity

During the 7-day reporting period following the first/single meningococcal vaccination, in the overall 2 to 10 years age population, across all vaccine groups, the most commonly reported systemic reaction was irritability, (range across vaccine groups, 11% to 22%), followed by: sleepiness (9% to 18%), change in eating habits (10% in all three vaccine groups), malaise (8% to 12%), headache (9% to 11%), myalgia (7% to 10%), and diarrhea (6% to 8%). No other systemic reaction was reported by more than 6% of the subjects in any vaccine group.

Table 26: Percentages of Children Ages 2 to 10 Reporting Any and (Severe)a Systemic Reactions after First/Single Meningococcal Vaccination, Days 1 to 7 and 1 to 3, Pooled Analysis

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

Source: module 5, section 5.3.5.3, ISS Tables, Table 12 and Table 15; *Headache, arthralgia, and rash were not collected in study V59P7, rash was only collected in study V59P20;
[a]Study V59P7 (only 2-5 years) collected systemic reactions as "present" or "absent" without grading severity; for the grading of severity in studies V59P8, V59P10, and V59P20 refer to Table 1.1.2-3 and Table 1.1.2-4;
[b]Percentage of urticarial rash;
[c]Fever: temperature (regardless of method of collection) ≥ 38°C, severe fever ≥ 39°C.

The two most commonly reported systemic reactions, irritability and sleepiness (both reported only in the 2 to 5 years age stratum), were reported by highest percentages after Menactra (22% and 18%, for irritability and sleepiness, respectively) and by lowest percentages after Menomune (11% and 9%, respectively). The reporting rates for irritability and sleepiness following administration of MenACWY (18% and 14%, respectively) were lower than those observed for Menactra but still higher than those observed for Menomune. The percentages of subjects reporting all other systemic reactions were similar across the three vaccines groups.

No severe systemic reaction was reported by more than 1% of the subjects in any vaccine group. Urticarial rash was reported by 2% of both MenACWY and Menactra recipients in study V59P20 (rash was solicited only in study V59P20).

Across the vaccine groups, in the majority of subjects, systemic reactions (any and severe) occurred within the first 3 days postvaccination: no more than a 3% difference in the percentages reporting systemic reactions of any severity was observed for days 1 to 7 vs. days 1 to 3; for the severe systemic reactions, the difference ranged between 0 and 1%.

No major difference in the percentages reporting fever (i.e., temperature [regardless of method of collection] ≥ 38°C) was observed across the three vaccine groups (days 1 to 7: range, 2% to 5%, days 1 to 3: range, 1% to 2%). Reports of severe fever (i.e., temperature [regardless of method of collection] ≥ 39°C) were low and similar across the vaccine groups (days 1 to 7 and 1 to 3: range, < 1% to 1%). No increase in the percentages reporting fever was observed when a second dose of meningococcal vaccine was administered in the 2 to 5 years age group.

Unsolicited Adverse Events

Unsolicited adverse events were discussed as follows:

(i) AEs reported within 1 month of the first/single vaccination: ages 2 to 10 years, comparing MenACWY (data pooled from all four studies) vs. Menactra (study V59P20) and Menomune (data pooled from studies V59P8 and V59P10);

(ii) AEs reported within 1 month of the second meningococcal vaccination in ages 2 to 5 years (for two injections of MenACWY, data pooled from studies V59P7 and V59P20; for Mencevax→MenACWY, study V59P7);

(iii) AEs reported during the 5-month follow-up period starting from 1 month after the last meningococcal vaccination, as follows:

   i. for MenACWY administered as a single injection: data pooled from studies V59P8, V59P10, and V59P20 vs. Menactra (study V59P20) and Menomune (data pooled from studies V59P8 and V59P10);
   ii. for two doses of meningococcal vaccine: two doses of MenACWY (data pooled from studies V59P7 and V59P20) vs. Mencevax→MenACWY (study V59P7).

Within 1 month of the first/single meningococcal vaccination, the most frequently reported unsolicited AEs irrespective of relatedness were similar for the MenACWY and comparator vaccine groups: cough, upper respiratory tract infection, pyrexia, and pharyngitis were reported by 2% of the subjects in at least one of the three vaccine groups; no other individual AE by preferred term was reported by more than 1% of the subjects in any vaccine group.

No AE assessed as at least possibly vaccine-related was reported by at least 1% of the subjects in any of the vaccine groups. The most commonly reported possibly related unsolicited AEs were the following local reactions ongoing past the 7-day observational period: injection site erythema, reported only

after MenACWY and Menactra (MenACWY: 11 subjects out of 3107; Menactra: seven subjects out of 1255) and injection site pruritus (MenACWY: four subjects out of 3107; Menactra: seven subjects out of 1255; Menomune: one subject out of 861.

The percentages of subjects reporting any possibly or probably related unsolicited AE after any vaccination throughout the studies were similar across the three vaccine groups (range, 3% to 5%). The only SOC affected by reports of possibly related AEs in at least 1% of the subjects across the three vaccine groups was "general disorders and administration site conditions" (total MenACWY: 59 subjects [2%], Menactra: 29 subjects [2%], Menomune: 10 subjects [1%]). In the analysis of the remaining SOCs, 19, 18, and 17 out of 3181 total MenACWY subjects reported at least possibly related AEs in the SOCs of "skin and subcutaneous tissue disorders", "nervous system disorders", and "gastrointestinal disorders", respectively. No other SOC was affected in more than ten out of 3181 total MenACWY subjects. In the comparator vaccine groups (Menactra, N = 1255; Menomune, N = 861) no SOC other than "general disorders and administration site conditions", mentioned above, was reported by more than ten subjects.

In the by age analysis of possibly related AEs, there were no major differences in the reporting rates observed across the vaccine and age groups. Across the two age groups, the reporting rates observed for MenACWY and Menactra recipients ranged between 4% and 5%, regardless of whether one or two doses of MenACWY were administered. The reporting rates for Menomune (2 to 5 years: 3%; 6 to 10 years: 2%) were slightly lower compared with MenACWY and Menactra, while the overall lowest percentage (1%) was observed among the 2 to 5 year olds who received Mencevax followed by MenACWY (N = 74).

In the analysis of individual SOCs, in both age strata, the only SOC affected by reports of possibly related unsolicited AEs in more than 1% of the subjects across all vaccine groups was "general disorders and administration site conditions (range across the age and vaccine groups, 1% to 2%).

Serious adverse events and deaths

Deaths

No death occurred in any of the four studies used to support this application.

Serious adverse events

Throughout the studies, in the overall 2 to 10 years population, no more than 1% of the subjects reported SAEs across the total MenACWY and comparator Menactra and Menomune groups. One of the SAEs reported, an episode of febrile convulsion, experienced by a MenACWY subject in the 2 to 5 years age stratum in study V59P10, was judged as at least possibly vaccine-related. An additional SAE (study V59P10, subject number 20/568, post-vaccine tonic convulsion) was considered by the investigator as not related to the vaccine itself but related to the conduct of the study (i.e., to the "act of vaccination"). The duration of the SAE was one day, the severity was mild, and the subject recovered. The event was assessed by the investigator as not related to the vaccine itself but related to the study conduct (i.e., the "act of vaccination").

When a single dose of meningococcal vaccine (MenACWY, Menactra, or Menomune) was administered, reports of SAEs were infrequent across the vaccine and age groups (range <1% to 1%). In the pooled analysis, reports of SAEs were more frequent when two doses of meningococcal vaccine were administered in the 2 to 5 years age group (3% and 12% in the MenACWY-->MenACWY and Mencevax--> MenACWY groups, respectively). This was accounted for in part by the fact that the

overall reporting period for the subjects receiving two vaccinations was longer compared with the reporting period for the single vaccination groups (8 to 18 months vs. 6 months). The more relevant explanation can be discerned from the by study analysis. When the MenACWY--> MenACWY group was analysed separately for studies V59P7 and V59P20, the percentage of subjects reporting SAEs in study V59P7 (8%) was higher than the respective percentage observed in study V59P20 (1%) and in line with the percentage observed in the comparator, Mencevax--> MenACWY group in study V59P7 (12%). The higher percentages reporting SAEs in study V59P7 were accounted for by a comparatively high incidence of varicella infection in this unvaccinated population and the fact that all varicella cases, regardless of severity and hospitalisation status, were categorised by the investigator as SAEs. In the large V59P20 study, when a two dose regimen was explored in the 2 to 5 years age stratum, the percentage of subjects reporting SAEs was the same (1%) regardless of whether one of two doses of MenACWY were administered.

Laboratory findings

N/A

Safety in special populations

Overall, no major or consistent differences in the safety profile of MenACWY were observed across the two age strata (2-5, 6-10 years) and by gender. The differences in the reporting rates for local reactogenicity systemic reactions and other indicators of reactogenicity after MenACWY observed across the three studies conducted in different geographic locations did not show any consistent pattern.

Immunological events

N/A

Safety related to drug-drug interactions and other interactions

In the limited sample size of only 74 subjects from study V59P7 who received Mencevax followed by MenACWY, no vaccine-vaccine interactions in terms of solicited reactions or unsolicited AEs was observed.

Discontinuation due to AES

No subject discontinued because of adverse events.

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 show 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.

Discussion on clinical safety

The presence of the protein to which the antigens are conjugated, and consequently the higher immunogenicity, could potentially explain the increased reactogenicity seen with MenACWY and Menactra compared to Menomune.

In the studies related to this variation application, including over 3000 subjects, one SAE that was considered possibly related to vaccination with MenACWY occurred (febrile convulsion in a 5 year old girl with a history of febrile convulsions) and one SAE related to the act of vaccination: tonic convulsion with enuresis in a 7 year old girl.

Regarding seizures/convulsions and Kawasaki disease, no new information was identified, but these AE terms should remain under close monitoring.

Conclusions on clinical safety

MenACWY was well tolerated in 3181 children (2-10 years) included in the integrated safety analysis. No new safety signals were observed.

2.4. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk management plan

The MAH submitted an updated Risk Management Plan within this variation procedure.

- ***Safety Specification – Non-clinical***

MenACWY formulations demonstrated an immune response in mouse immunogenicity and rabbit toxicology studies. The toxicology studies investigated general toxicology, local tolerability, and reproduction and embryofoetal development toxicity in rabbits. The general toxicology dose regimen of 5 doses exceeds the single dose clinical regimen.

In conclusion, MenACWY vaccine was well tolerated and immunogenic in rabbits after one or five IM administrations at a dosage which, on a body weight basis, was more than 24 times greater than the anticipated human dose. Further, the dosing regimen used in the multiple-dose portion of this study exceeded the planned clinical regimen by two to four administrations. No systemic toxicity occurred and only slight and reversible inflammation limited to the injection sites was noted.

There were no effects on embryofoetal development in the pilot rabbit reproductive and developmental toxicity study when one to two times the clinical dose was administered three times pre-gestation and twice during gestation. There were no effects on reproduction, embryofoetal and postnatal development in the definitive rabbit study when the clinical dose was administered three times pre-gestation and twice during gestation, thus representing, on a body weight basis, a 15-fold multiple of a human dose and an excess by two to four administrations versus the planned clinical regimen.

Summary of safety concerns from nonclinical investigations

SAFETY CONCERN (from nonclinical studies)	RELEVANCE TO HUMAN USAGE
Repeat Dose Toxicity:	
Transient inflammation of the injection sites. There were no other histopathology findings.	Novartis MenACWY administration resulted in comparable local reactogenicity rates compared with licensed comparators (e.g., Menactra, Boostrix) which were mostly mild in severity and of limited duration.
Reproductive Toxicity	
No test article-related maternal findings.	
Developmental Toxicity	
No fetal alterations related to the test article.	

- ***Safety Specification – Clinical***

The safety specification has considered the most important issues identified, suspected or missing during the development programme (see summary of the EU risk management plan).

The MAH is proposing additional pharmacovigilance activities through questionnaires for Guillain-Barre Syndrome, Acute disseminated encephalitis, Kawasaki Disease and Vasculitis. Vaccine failure will be closely monitored.

- ***Proposed pharmacovigilance activities/studies***

Study V59_34OB

Study V59_34OB is a phase IV study to assess the safety of MenACWY being used by a large Healthcare Maintenance Organization (HMO) subjects 11 to 20 years of age in the United States. The study is a post-marketing study which evaluates the safety of MenACWY for a predetermined set of events of interest (EOI) among 50,000 vaccinated adolescents. Subjects who have been vaccinated with MenACWY and have experienced an incident EOI within the one year observation period following vaccination are selected for the primary analysis using the self-controlled case-series methodology to determine the relative incidence of each EOI. The 26 EOI comprise certain neurological, immunological, vascular, musculoskeletal, and hematologic disorders and are commonly evaluated adverse events in vaccine safety studies. In a secondary objective, relative incidence of the EOI will also be determined by first estimating the incidence rates for EOI from the current study and, second, comparing these to published literature incidence rates from comparable populations, where available.

This study started in September 2011 and enrolment will continue for a minimum of one year or until 50,000 subjects have been vaccinated.

Study V59_54OB

Study V59_54OB is an open label, descriptive, epidemiological safety surveillance study of MenACWY in subjects 2 to 10 years of age. The study is enrolling in the same large HMO where study V59_34OB is being conducted and is in two parts. Part I begins with the first administration of MenACWY to a child

2 through 10 years of age (inclusive) who receives medical care at the site where the study is being conducted. Part I continues for 3 years or until the beginning of Part II, which ever occurs first. Part II of the study will be initiated if there is a recommendation by ACIP for routine use of MenACWY in at least one birth cohort that is within the 2 to 10 year age range.

Kawasaki disease

The estimated annual incidence rate of 38 per 100,000 is of concern since it is higher than the expected rate (2.5 - 9 cases per 100,000 in EU). However since these estimates are based on very low absolute number of cases, the observed incidence rates should be interpreted with caution. There are indications that the geographical location of study population greatly influences the KD incidence rates. The involvement of a KD expert panel to define disease criteria is strongly endorsed. A latency period of up to 30 days between vaccination and onset has been postulated as reasonable criteria for relatedness. This cut-off has been substantiated by literature and is accepted. It is recognised that due to the low EU background incidence in the 2-10 age group (2.5 - 9 cases per 100,000 children <5 years of age) combined with the limited use of the vaccine in 2-10 years of age population, obtaining a sufficient number of vaccinated and unvaccinated KD cases may be impossible. It is agreed that increased follow-up of the reported cases is most important and feasible at this stage. The enhanced PhV activities (*i.e.* KD questionaire) are endorsed in combination with close monitoring of any new reports.

Translucent particles in the syringe/vial formulations

The presence of oily and translucent visible particles was detected in the syringes and communicated to the EMA in February 2011. Analyses of the particles revealed that they are composed by silicone oil and proteins. The MAH has performed a series of experiments with the goal of identifying the potential interactions between the translucent particles and glycoconjugate present in the PFS and has also performed additional MFI analysis to better elucidate the presence or absence of any time-based trend. There does not appear to be an interaction that would affect dose strength and there does not appear to be a clear time-based trend that could impact product quality over time. Additionally, MFI analysis of samples in the vial/vial presentation show significantly lower particle counts and confirm that the presence of silicone oil is responsible for the translucent particles observed in PFS.

It is concluded that the translucent particles have been present in the pre-filled syringe drug product all along, and that from a pharmacological-toxicological viewpoint the presence of polydimethylsiloxane does not raise a serious concern, and hence there is no immediate need for market action nor an immediate need to uphold the release of new pre-filled syringe batches.

A monodose vial/vial presentation will be introduced in the EU market. The MAH confirmed that the syringe/vial presentation will not be marketed for children below 11 years and proposed the following actions:

- The MAH will pack only vial/vial presentation with leaflet including the 2-10 indication. No syringe/vial presentation will be released onto the market for children below 11 years. All European markets will have switched to Menveo vial/vial presentation by the end of March 2012. After the end of March 2012 the company will no longer release the PFS/vial presentation into the distribution chain for any age group indication.

- Since no additional PFS/vial presentation will be released into the market after March 2012, all of the PFS/vial presentations remaining on the European market will be expired by August 2013.

Table 1. Summary of the risk management plan (including the changes related to the application presented highlighted)

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 pharmacovigilance 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

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 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
Study V59_53, co-administration of Menveo with travellers vaccines	Final CSR: By the end of 2012

2.5. Changes to the Product Information

The MAH proposed the following changes to the Product Information (PI), to which the CHMP agreed for the vial/vial presentations (EU/1/10/614/002, EU/1/10/614/003):

Update of sections 4.1, 4.2, 4.5, 4.8 and 5.1 of the SmPC in order to extend the indication to include children aged 2 to 10 years old at risk of exposure to Neisseria meningitidis groups A, C, W135 and Y.

During the procedure, the CHMP requested further amendments to the PI as discussed in detail above (see discussion on clinical efficacy):

Update of section 4.4 of the SmPC to include a warning that booster dose should be considered for persons who remain at risk of exposure to Men A.

The Package Leaflet is updated in accordance.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, which were reviewed by QRD and accepted by the CHMP.

Annex II was updated to reflect the obligation to complete the following post-authorisation measure:

Study to evaluate immediate and longer term antibody titres elicited by one or two doses of Menveo administered in children aged 2-10 years according to a CHMP-agreed protocol.

2.6. User consultation

A justification for not performing a consultation with target patient group has been submitted. The MAH submitted a user consultation with patients groups for a corresponding product Menjugate. When applying for the marketing authorisation the applicant submitted the user test for Menjugate. A bridging document indicating the similarities and differences between the package leaflet for Menjugate and the package leaflet for Menveo was provided at the time of the initial marketing authorisation. The justification is considered accepted.

3. Benefit risk assessment

Benefits

Due to the low incidence rates of MenACWY disease it is not considered feasible to generate clinical efficacy data for licensing, the evaluation of efficacy was based upon 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. 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 less common in Europe (A, Y and W-135).

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. The use of plain polysaccharide meningococcal ACWY vaccines is limited to children over 2 years of age.

In the main pivotal study (V59P20) for this variation application the seroresponse (95%CI) one month following a first dose with MenACWY was 72% (68-75), 60% (56-64), 72% (68-75) and 66% (62-70) for serogroups A, C, W and Y respectively for children aged 2-5 years. The response for children aged 6-10 years was 77% (73-80), 63% (59-67), 57% (53-61) and 58% (54-62) respectively. Non-inferiority to Menactra, a conjugated MenACWY vaccine, was established for all serogroups except A, where the difference in response was - 6% (95%CI: -11 to -1). One month after a first dose 72%, 68%, 90% and 76% of children between 2 and 5 years had hSBA ≥1:8 for serogroups A, C, W and Y respectively. For children aged 6 – 10 years this was slightly higher at 77%, 77%, 91% and 79% respectively.

One month following a second dose the percentage of children aged 2 to 5 years with hSBA ≥ 1:8 was 91%, 99%, 99% and 98% for serogroups A, C, W and Y respectively.

The response with MenACWY was compared to the response to a plain PS MenACWY vaccine in studies V59P7, V59P8 and V59P10. In study V59P7 the percentage subjects (aged 3-5 years) with hSBA ≥1:8 with MenACWY 28 days after the first dose was 61%, 54%, 84% and 67% for serogroups A, C, W and Y respectively. The % of subjects with hSBA ≥1:8 following a plain PS vaccine was 39%, 39%, 59% and 57% respectively. In study V59P8 the % of subjects (aged 2-10 years) with hSBA≥1:8 one month following MenACWY in children was 80%, 73%, 92% and 88% for serogroups A, C, W and Y

respectively compared to 37%, 55%, 65% and 55% following a single dose of Menomune for serogroups A, C, W and Y. Superiority of MenACWY over Menomune was demonstrated. In study V59P10 the seroresponse one month following MenACWY in children aged 2-10 years was 93%, 82%, 74% and 82% for serogroups A, C, W and Y respectively. The seroresponse one month following Menomune was 55%, 52%, 46% and 63% for serogroups A, C, W and Y respectively. Here too, superiority of MenACWY over Menomune was demonstrated.

Six months after a single dose MenACWY in study V59P7 the percentage of subjects with hSBA ≥1:8 was 10%, 32%, 77% and 60% for serogroups A, C, W and Y respectively. Six months after a single dose in study V59P10 (children 2-10 years) the % of subjects with hSBA ≥1:8 was 35%, 81%, 96% and 89% for serogroups A, C, W and Y respectively. Twelve months after a single dose MenACWY in study V59P7 the % of subjects with hSBA ≥1:8 was 9%, 24%, 76% and 64% for serogroups A, C, W and Y respectively. Twelve months after a single dose MenACWY in study V59P8 the % of subjects with hSBA ≥1:8 was 23%, 53%, 90% and 77% for serogroups A, C, W and Y respectively. The five year persistence data of study V59P20E1 are expected in 2013.

Data from studies where booster dose has been administered support the ability of Menveo to induce a T-cell-dependent primary immune response. These data predict that a memory response will be elicited.

Uncertainty in the knowledge about the beneficial effects

No data on prevention of meningococcal disease have been generated for MenACWY.

There is data on the immune response following a second dose in children aged 2-5 years (V59P20), which indicates a considerable increase in immune response in this age group. There is no data related to a second dose for children aged 6-10 years; however as their immune response following a single dose is only slightly higher than in children aged 2-5 years a second dose could be of additional benefit there too.

There is persistence data up to 12 months following a single dose which indicates the need for a booster dose as the persistence of especially serogroup A is poor when measured with the hSBA. For serogroup C persistence of bactericidal antibodies is moderate. This is not confirmed by rSBA results in adolescents, where a high rSBA response was still seen after 3 years. There is uncertainty about the reliability of the rSBA results for persistence of MenA as a high proportion of unvaccinated persons also had rSBA ≥1:128 in study V59P13E1. There is no insight in persistence following a booster dose. Neither is there insight in persistence of bactericidal antibodies following two doses in children aged 2 to 10 years.

MenACWY has not been evaluated in immunocompromised people.

There is no data on efficacy and safety in children with complement disorders or with functional or actual asplenia.

No data on co-administration of MenACWY with other vaccines has been provided for the 2-10 year age group. Possible interactions with other commonly used travellers vaccines are being investigated in adults/adolescents.

Risks

Unfavourable effects

The safety database includes more than 3000 subjects 2-10 years of age who received at least one Menveo dose. In addition a safety database comprising more than 7000 infants/toddlers have been submitted and finally there is considerable experience from the use of Menveo in adolescents and adults. Overall, it appears that reactogenicity of Menveo is acceptable and slightly increased compared to unconjugated MenACWY vaccines.

Following a single/first dose pain was the most commonly reported local reaction, and was reported by 31%. Severe pain was reported by ~1%. The most commonly reported systemic reaction was irritability (18%) followed by sleepiness (14%), and malaise (12%). The most frequent reported unsolicited adverse events (within 1 month of a single/first dose) were cough, upper respiratory tract infection, pyrexia, and pharyngitis (reported by ~2% of subjects). No deaths occurred. One SAE possibly related to MenACWY occurred, febrile convulsion in a 5 year old child with a history of convulsions. There were no discontinuations due to AEs in the 2-10 year population.

Uncertainty in the knowledge about the unfavourable effects

MenACWY has not been evaluated in persons with thrombocytopenia, bleeding disorders or that are receiving anticoagulant therapy.

Benefit-risk balance

Importance of favourable and unfavourable effects

At present no conjugated tetravalent MenACWY vaccines are licensed in the EU for children aged 2-10 years. The presence of additional serogroups compared to available conjugated meningococcal vaccines ensure that MenACWY provides broader protection (to A, W and Y) in settings where this would be necessary, which is an important benefit to those children expected to travel to areas where they would be at increased risk. As plain polysaccharide vaccines are known to be less effective in infants and young children, and as they do not mount a booster response, the benefit of having a conjugated tetravalent meningococcal vaccine is considered large for those children at risk of exposure. Indeed, superiority of MenACWY was mostly demonstrated over different plain polysaccharide vaccines and the MAH has demonstrated that a good booster response can be achieved, which are important benefits over the currently available polysaccharide vaccines.

Overall the safety profile is quite favourable, and no unknown risks were identified.

Benefit-risk balance

Although the benefit of having a conjugated tetravalent meningococcal vaccine available for young children travelling to areas where they are at increased risk of exposure and thus of invasive disease is considered quite large, it is crucial that when vaccinated, optimum protection should be achieved in these children.

The immune response following one dose is largely superior to the immune response after a single dose of licensed tetravalent unconjugated vaccines, reactogenicity is only slightly increased, and unlike unconjugated vaccines MenACWY elicits a T-cell dependent immune response, therefore the overall Benefit Risk of a single dose of MenACWY in children aged 2-10 years is positive.

Nonetheless, results from study V59_57 are needed to determine the added benefits of a second dose versus the increased risks.

Discussion on the benefit-risk assessment

The overall seroresponse to MenACWY is moderate: the response to serogroup C is approximately 60% for all ages, around 70% to the other three serogroups in the younger age group and around 60% for serogroup W and Y in the older age group, and almost 80% in for serogroup A in the older age group. This appears mostly driven by a low response in those with baseline hSBA≥1:4, in which the response is clearly less than in those without baseline antibodies (especially for serogroups W and Y). However, there is sufficient evidence demonstrating the boosterability of MenACWY. Importantly, the percentage subjects that achieved hSBA≥1:8 following vaccination regardless of baseline titres was higher.

No comparative study with monovalent MenC was made for children included in the current variation application. As a consequence, the indication is limited to persons "at risk of exposure", a term that was introduced to indicate that the B/R is so far positively established for EU individuals at risk of invasive disease, e.g. through travel or during outbreaks.

There are clear indications of improved immunogenicity with a second dose in children aged 2 to 5 years with possibly limited additional risks associated with a second dose. The MAH is planning a study (Study V59_57) to compare one versus two doses in children aged 2 to 10 years. The study shall provide additional information about the safety and immunogenicity and persistence of bactericidal antibodies following two doses as compared to one dose. These results are needed to determine the added benefits of a second dose versus any increased risks. The MAH should submit the results of this study as soon as they are available.

As with adults, adolescents and children over the age of 11, problems with persistence of antibodies against serogroup A are seen, and to a lesser degree with MenC. It appears that a booster dose is needed to maintain bactericidal Abs for serogroup A when relying on the hSBA data. However, this is not confirmed by the rSBA results in adolescents, where concerns exist on the reliability of the results for MenA. A warning has been included in the SmPC that there is a steep decline in antibodies and as such a booster dose should be considered for persons who remain at risk of exposure to MenA.

In 2 to 10 year olds, there currently is no long-term follow-up (> 1 year) and all data has been generated using the hSBA. The MAH has plans to follow-up the subjects from the larger phase 3 study V59P20 at a five year time point and this data will be available in 2013 from the extension study V59P20E1.

3.1. Conclusions

The B/R of Menveo, meningococcal ACWY conjugate vaccine (diphtheria CRM_{197} conjugate) in the indication of

> *Menveo is indicated for active immunization of children (2 to 10 years of age) 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*

is positive for the vial/vial presentations.

4. 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(s) accepted		Type
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Update of sections 4.1, 4.2, 4.5, 4.8 and 5.1 of the SmPC of the vial/vial presentations in order to extend the indication to include children aged 2 to 10 years old and consequential update of section 4.4 of the SmPC to include a warning that booster dose should be considered for persons who remain at risk of exposure to Men A. The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to revise the product information according to the QRD template.

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

This CHMP recommendation is subject to the following new conditions:

Conditions and requirements of the Marketing Authorisation

Risk Management System and PSUR cycle

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable

Obligation to complete post-authorisation measures

The MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
Study to evaluate immediate and longer term antibody titres elicited by one or two doses of Menveo administered in children aged 2-10 years according to a CHMP-agreed protocol.	Q4 2014

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

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 (SmPC) and, as appropriate, in the Package Leaflet.