



European Medicines Agency

ASSESSMENT REPORT

FOR

Menveo

Common Name:
Meningococcal Group A, C, W135 and Y Conjugate vaccine

Procedure No. EMEA/H/C/001095

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Novartis Vaccines and Diagnostics S.r.l. submitted on 31 October 2008 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Menveo, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The legal basis for this application refers to:

A - Centralised / Article 8(3) / New active substance.

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

The applicant applied for the following indication: Menveo is 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.

Information on Paediatric requirements:

Pursuant to Article 7, the application included an EMA Decision P/103/2008 for the following condition:

- *Meningococcal meningitis*

Invasive disease caused by *Neisseria meningitidis* groups A, C, W135 and Y

on the agreement of a paediatric investigation plan (PIP)

The PIP is not yet completed.

Scientific Advice:

The applicant received Scientific Advice from the CHMP. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

CHMP (Scientific) Advice was given on several occasions:

- EMA/CHMP/SAWP/501998/2006 (dd. 2006-12-14) (*initial SA regarding quality, non-clinical and clinical aspects*)
- EMA/CHMP/SWAP/155074/2007 (dd. 2007-04-26) (*Follow-up S.A. on clinical development plan in children aged 2 – 10 years*)
- EMA/231862/2007 (dd. 2007-05-31) (*Clarification letter of follow-up S.A.*)
- EMA Pre-submission meeting (2008-06-12)

Licensing status:

The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 31 October 2008.
- The procedure started on 19 November 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 5 February 2009. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 6 February 2009. In accordance with Article 6(3) of Regulation (RC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- During the meeting on 16-19 March 2009, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 19 March 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 July 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 7 September 2009.
- During the CHMP meeting on 21-24 September 2009, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The summary report of the inspection carried out at the following site(s) Novartis Vaccines and Diagnostics S.r.l Bellaria-Rosia 53018 Sovicille (Siena) Italy between 14 and 18 September 2009 was issued on 3 December 2009.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 16 November 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 30 November 2009.
- During the meeting on 14-17 December 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Menveo on 17 December 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 17 December.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Meningococcal disease forms a leading cause of bacterial meningitis and sepsis in both industrialised and developing countries worldwide. The causative agent is a gram-negative bacterium: *Neisseria meningitidis*. Asymptomatic colonization of the upper respiratory tract by encapsulated *N.meningitidis* is common, however, only a small percentage of colonized persons develop disease (Vogel, 2001). In Europe, incidence rates of meningococcal disease have been found in the range of 0.4 to 4.9 cases per 100.000 inhabitants per year (Roberts *et al.*, 2007). Invasive infection by *N.meningitidis* usually manifests as bacteraemia and/or meningitis, and less commonly as septic arthritis, myocarditis, pericarditis, endophthalmitis, or pneumonia (Stephens *et al.*, 2007). Other signs of meningococcal meningitis may include headache, stiff neck, fever, chills, malaise, and shock. The case-fatality rate for meningococcal disease ranges from 2% to 40%, being highest in patients with meningococemia and lowest in patients with mild forms of bacteraemia or uncomplicated meningitis (Andersen, 1978 & Greenwood *et al.*, 1987).

At least 13 meningococcal serogroups have been identified based on differences in capsular polysaccharides. Five serogroups (A, B, C, Y and W135) are responsible for the vast majority of cases of meningococcal disease worldwide. The distribution of these serogroups varies by geographic region. Serogroup B and C strains are currently the most prevalent in Europe, and B, C and Y in North America, (Stephens *et al.*, 2007; Roberts *et al.* 2007). Serogroup A strain is common in developing countries (Greenwood, 1987). Serogroup W135 outbreaks have been reported in several countries among pilgrims attending the Hajj (yearly pilgrimage to Medina & Mekka), and close contacts (Sandell *et al.*, 2001; Aguilera *et al.* 2002; Hahne *et al.*, 2002; Taha *et al.*, 2002).

Meningococcal disease is predominantly a disease of infants and young children (6 months–2 years), due to acquisition of natural immunity from around 2 years onwards. The presence of maternal antibodies provides neonates with passive immunity. Increased disease incidence can also occur in adolescents and adults. Disease among adolescents and young adults is more a consequence of social behaviour. A known risk factor for meningococcal disease is clustering of individuals, which potentially results to quick transfer strains. This is believed to explain high rates of meningococcal disease among new military recruits during basic training prior to the institution of routine vaccinations, and among matriculating college students residing in dormitories (Goldschneider *et al.*, 1969a; Goldschneider *et al.*, 1969b; CDC, 2000; Bruce *et al.*, 2001). Additionally, persons travelling to regions where other serogroups are circulating are at increased risk of meningococcal disease, as illustrated by outbreaks of meningococcal disease due to serogroup W135 following the Hajj in 2000 .

Meningococcal polysaccharide vaccines (based on purified meningococcal capsular polysaccharides) are available for prevention of disease caused by serogroups A, C, W and Y strains of *N.meningitidis*. Serogroup A & C polysaccharides are safe and immunogenic, with clinical efficacy rates of 85% and higher among children aged 5 years or older, and adults. Serogroup Y & W135 polysaccharides are also safe and immunogenic in older children and adults, although clinical protection has not been documented (Rosenstein *et al.*, 2001). A major downfall of the polysaccharide vaccines is their relative ineffectiveness in young children, and the short duration of protection if achieved in these age groups (CDC, 1997). In addition, studies have suggested that multiple doses of serogroup A & C polysaccharides may cause immunologic tolerance (Granoff *et al.*, 1998; MacLennan, *et al.* 2001).

The possibility of immunologic hyporesponsiveness following repeated exposure to unconjugated meningococcal polysaccharide vaccines is of potential concern. This has been described among infants and older individuals for serogroup C meningococci, but also for other than serogroup C meningococcal polysaccharides (MacLennan *et al.*, 1999; Granoff *et al.*, 1998; Richmond *et al.*, 2000; Keyserling *et al.*, 2005).

Unlike meningococcal polysaccharide vaccines, vaccines conjugated to a protein antigen are thought to be immunogenic in young children and infants with more durable immunity, due to the conversion of the immune response from a T-cell independent to a T-cell dependent one (Käyhty *et al.*, 1994; Dintzis *et al.*, 1994). This has been demonstrated for conjugate *H influenzae* type B vaccines, and similar properties apply to licensed *Streptococcus pneumoniae* protein-conjugate vaccine and for the existing *N meningitidis* serogroup C conjugate vaccine (Granoff *et al.*, 1998; Obaro *et al.*, 2006). Data currently available from the UK and Canada, estimate the clinical effectiveness in adolescents for the meningococcal serogroup C conjugate vaccine at 88% to 96% (Trotter *et al.*, 2004; DeWals *et al.*, 2007). A study from Spain estimated the effectiveness among children below 10 years of age at 94% (Larrauri *et al.*, 2005).

About the product

Novartis Meningococcal ACWY conjugate vaccine (Menveo) belongs to the pharmacotherapeutic group of Meningococcal vaccines (ATC code: JO7AH). It is composed of four drug substances, MenA-CRM₁₉₇, MenC-CRM₁₉₇, MenW135-CRM₁₉₇ and MenY-CRM₁₉₇. The vaccine is presented in the form of one vial containing the lyophilised MenA Conjugate Component plus excipients, and one syringe containing the

liquid MenCWY Conjugate Component plus excipients. The selected final formulation is made of 10-5-5-5 µg per oligosaccharide of *N. meningitidis* serogroups A, C, W, and Y respectively, conjugated to Cross-Reactive Material protein (CRM₁₉₇) of *Corynebacterium diphtheria* per dose (0.5 ml). The pharmaceutical form is powder and solution for solution for injection. The vaccine contains no adjuvant, thiomersal or preservatives.

Within Europe, Menveo would be intended for individuals at increased risk of invasive meningococcal disease, such as travellers and individuals clustered together in close proximity (including matriculating university students and those in military service).

The proposed **therapeutic indication** is:

“Menveo is 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.”

Posology:

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

2.2 Quality aspects

Introduction

Menveo (Meningococcal Group A, C, W135 and Y Conjugate Vaccine) consists of one vial, containing the lyophilized MenA Conjugate Component, and one syringe containing the liquid MenCWY Conjugate Component. The selected final formulation contains 10-5-5-5 µg per oligosaccharide of *N. meningitidis* serogroups A, C, W, and Y respectively, without adjuvant. The pharmaceutical form is powder and solution for solution for injection. The dose is 0.5 ml (after reconstitution).

Menveo consists of 4 drug substances: Meningococcal group A (or C, or W 135 or Y) oligosaccharides conjugated to *Corynebacterium diphtheriae* CRM₁₉₇ protein (abbreviated to MenA-CRM, MenC-CRM, MenW-CRM or MenY-CRM Conjugate respectively). Each drug substance is prepared from two purified intermediates derived from bacterial fermentation:

Corynebacterium diphtheriae Cross Reactive Material 197 (CRM₁₉₇) and capsular polysaccharide obtained from either *Neisseria meningitidis* serogroups A, C, W135 or Y.

In summary, the drug substance part of Module 3 consists of nine separate sections, which are:

- CRM197 (process intermediate)
- MenA polysaccharide (process intermediate)
- MenC polysaccharide (process intermediate)
- MenW polysaccharide (process intermediate)
- MenY polysaccharide (process intermediate)
- MenA-CRM Conjugate (drug substance)
- MenC-CRM Conjugate (drug substance)
- MenW-CRM Conjugate (drug substance)
- MenY-CRM Conjugate (drug substance)

The drug product part consists of 2 separate sections:

- MenA Lyophilized Conjugate Component (MenA Lyo)
- MenCWY Liquid Conjugate Component (MenCWY Liquid)

Active Substance

The tetravalent MenACWY conjugate vaccine consists of oligosaccharides derived from capsular polysaccharides of *Neisseria meningitidis* serogroups A, C, W and Y, each conjugated to the CRM₁₉₇ carrier protein.

Meningococcal polysaccharide is produced from the fermentation and purification of the Gram-negative diplococcus *Neisseria meningitidis* serogroup A, C, W or Y.

CRM

The manufacturing of CRM₁₉₇ is carried out at the Bellaria-Rosia site and testing occurs both at this and the Siena site.

- Manufacture:

The production of purified CRM₁₉₇ starts with the fermentation of *Corynebacterium diphtheriae* C7B197M8. CRM₁₉₇ is secreted into the supernatant. The supernatant is collected by continuous centrifugation and filtered through a (stacked disk) depth filtration. The filtrate is concentrated and diafiltered against sodium phosphate buffer, followed by filtration through a 0.22 µm filter. Further purification includes column chromatography. The eluate is ultrafiltered and diafiltered against potassium phosphate buffer. The retentate is collected, a stabilizer is added and the purified CRM bulk concentrate is filtered at 0.22 µm and stored at < -15°C.

- Control of materials

New master and working seeds were produced to minimize the risks of contamination with Transmissible Spongiform Encephalopathies (TSE) by ensuring that all possible material of bovine origin had been removed from the seed production process wherever possible. This involved changing to CY medium. The specifications for MS and WS are in agreement with Ph Eur requirements.

Most materials used in the production are of pharmacopoeia (Ph. Eur or USP) quality. For others internal specifications are set.

- Process validation

All process requirements were met for three consecutive full scale runs plus two additional runs. A tabulated summary of each of the steps of the process outcomes was given and demonstrates consistency.

Consistency is demonstrated for the unmodified process that was used for the clinical and consistency batches. This data support the acceptance criteria. After that post-validation changes have been made to the process.

- Manufacture process development

The CRM₁₉₇ manufacturing process used for MenACWY conjugate vaccine production is based upon Novartis Vaccines' previous experience with this protein. The development and optimization of the manufacturing process were conducted and implemented at Novartis Siena. Subsequently the process was transferred to the Rosia site where it was validated and the phase 3 clinical batches were produced.

The production process for purification of CRM is acceptably controlled and has been validated with batches of the same sizes as batches intended for commercial production. The quality control of CRM complies with Ph. Eur., and is performed with validated methods.

The results from the batch analysis for purified CRM show that all batches are within the pre-set specifications and show a high degree of consistency. Submitted stability data for CRM support the proposed shelf-life of 30 months.

However, changes were made to the CRM197 manufacturing process after the completion of the process validation. Material from this proposed modified process was not used in the clinical studies. Upon request the company has submitted data to demonstrate comparability between the validated and modified process which has demonstrated that the modified process does not affect the impurity profile. The company has already started a 36 months stability study for CRM197 produced with the commercial process at Rosia.

Meningococcal Polysaccharides and conjugates

- **Manufacture**

The production of the Meningococcal Polysaccharides and conjugates of the different serotypes is very similar and differs just in a few aspects.

Batches and scale definition

A batch of Men polysaccharide is defined as the product of a single fermentation and harvest. All Men polysaccharide fermentation and purification clinical lots were produced at the full-scale defined for commercial production lots.

Fermentation of Polysaccharides

Vials of working seed are incubated in flasks until appropriate OD₅₉₀ is reached.

The flasks of bacterial suspension are then inoculated in the fermentor. The fermentation proceeds at a controlled conditions. At the end of fermentation, the culture is inactivated by addition of formaldehyde and incubated.

The supernatant is collected by continuous (stacked disk) centrifugation and serially depth-filtered to remove material in suspension. This supernatant is concentrated and diafiltered against WFI. Polysaccharide is precipitated from the retentate by the appropriate reagent solution. The precipitate (humid paste) is collected by centrifugation and stored at $\leq -15^{\circ}\text{C}$ in polypropylene containers.

Purification of Polysaccharides

Thawed paste (humid paste) is added to alcohol and then the clarified extract is 0.22 μm filtered.

The alcoholic suspension is filtered, precipitated and the precipitate is recovered by centrifugation.

The polysaccharide vacuume dried after previous centrifugation.

The purified polysaccharide is a process intermediate, stored in a polypropylene container at -15°C or below.

Preparation of Men-CRM.

Purified polysaccharide Men is subsequently hydrolyzed, sized, activated and conjugated to the carrier protein CRM₁₉₇ to give the drug substance.

Sizing: Sizing of Men oligosaccharide utilizes three consecutive manufacturing steps: polysaccharide hydrolysis (to produce oligosaccharides of suitable average chain length), ultrafiltration (to remove high molecular weight oligosaccharides), and oligosaccharide sizing.

Activation: Activation of Men oligosaccharide utilizes four consecutive manufacturing steps: reductive amination (to introduce an amino group at the reducing end of the oligosaccharide), aminated oligosaccharide concentration/diafiltration (to remove excess reductive amination

reagents), rotary evaporation (to remove water), and finally oligosaccharide activation (to react the free amino group of the oligosaccharide with bis N-hydroxysuccinimide ester of adipic acid).

Conjugation: The drug substance Men-CRM is created by the conjugation of the activated Men oligosaccharide molecule to purified CRM197 protein.

Filling, storage and transportation (shipping)

The Men-CRM conjugate bulk is stored in sterile polyethylene terephthalate copolyester containers at $\leq -15^{\circ}\text{C}$.

The production of the four Meningococcal humid paste, purified polysaccharide and Men-CRM-conjugates is well described in separate sections.

Source, history, and generation of the cell substrate

For all four Meningococcal seeds a flow chart detailing the history of the master and working seed production from the initial receipt of the organism within Novartis is provided. In addition information regarding place of isolation of the strains, whether they are from invasive cases or healthy carriers, and typing (utilizing both immunological and molecular typing scheme) is provided.

The seeds for Menveo were produced to ensure that all material of bovine origin was removed from the seed production process. In order to reduce TSE risk, a series of subculturing operations were performed on media sourced in compliance with EMEA 410/01 and 9 CFR 94.18.

The retest of master and working seeds is carried out in accordance with an internal procedure. The colony count, which has been selected as the most critical parameter, shows no downward trend for any of the master seeds and working seeds used for production of Menveo.

In general, the control testing of the Master and Working cell banks is considered acceptable. Novartis has committed to submit batch analysis results for three commercial batches of purified polysaccharide produced with the new Men A working seed.

Summary of polysaccharide and Men-CRM production

Compendial (Ph. Eur., USP or ACS) specifications are in place for most of the raw materials used in the routine production. However, the internal specifications for raw materials for which non-compendial in-house specification have been set are too vague and not acceptable. The CHMP agreed to the applicant's commitment to provide this as a follow-up measure. The water for injection and purified water are in compliance with Ph.Eur or USP.

The only ruminant derived materials used are derived from bovine milk sourced from healthy animals in the same conditions as milk considered fit for human consumption and therefore complies with the TSE Note for Guidance (EMEA/410/01 Rev. 2). No viral issues have been identified.

Overall the production of all polysaccharides, CRM and Men-CRM conjugates is consistent. Process outcomes are identified as critical and non-critical. It is noted that the company's definition for a non-critical process control parameter contains internal inconsistencies concerning whether or not these parameters impact quality characteristics. The applicant has committed to revise the relevant SOP.

The Manufacturing process for purified polysaccharides is for most steps acceptably controlled and have been validated with batches of the same size as batch sizes intended for commercial production.

However, alert limits set for bioburden during early purification steps for the polysaccharides were considered too high. The root cause of the high bioburden observed during validation is likely related to the design of the product recovery line. After implementing operational improvements significantly lower general bioburden levels were found in the subsequent manufacturing campaign. An acceptable lower

lower action limit for bioburden, applicable to all four serogroups have been set. Additional modifications to the manufacturing process in order to reduce the general bioburden level even further, also on request from the GMP inspection (see below) will be introduced. The company has committed to undertake the re-assessment of the action limit for the general bioburden when data from 25 lots of each serogroup are available. Furthermore, the Applicant has committed to submit interim data from the first 5 batches of each serogroup and set preliminary action limits for bioburden based on these results (expected in 2012). In order to verify the effect of the final improvements introduced in 2009, the company has also committed to provide data from bioburden testing for the first five consecutive lots regardless of serogroup. Finally, the Company has committed to inform the authorities of any out of specification results or negative trends observed with regard to bioburden results.

It was discovered, as part of a follow-up to a corrective and preventive action initiated by an out of specification result, that the established formaldehyde inactivation was not able to completely inactivate 100 % of the *N. meningitidis*. The Company has therefore changed the acceptance criteria for specific bioburden after revalidation of the inactivation step. The Company has adequately demonstrated that even though the formaldehyde inactivation is not capable of consistently inactivating 100% of the *N. meningitidis*, the successive process steps, will sufficiently remove or inactivate residual viable *N. meningitidis*. This has been verified by the re-validation of the process.

A product and process-related inspection of the site Novartis, Rosia - Sovicille (SI) - Italy was requested at D120 of the procedure to examine the assessment issue raised on the bioburden in the Active Substance manufacturing process. It is concluded that the activities required to fully solve all the points raised during the GMP inspection required time, however the site can be accepted for manufacturing Menveo provided that: An interim report is provided not later than three months updating on the progress of the resolution of open deviations. A further inspection will be carried out with a timeline for reporting by September 30th, 2010.

Quality control of purified polysaccharides are performed with adequately validated methods and are in general considered to be in compliance with the Ph. Eur. monographs for Meningococcal polysaccharide vaccine and Meningococcal group C conjugate vaccine. However, the method used for determination of the molecular size distribution are slightly different from the Ph. Eur. method, but is based on the same principle. This deviation is considered acceptable as the purified polysaccharides are intermediates which are hydrolysed later in the process. The deviation of the test for sialic acid from the Ph. Eur. method is justified.

In general, the results from the batch analysis of each of the four polysaccharides demonstrate consistency and were within the pre-set limits.

The manufacturing of conjugates is considered satisfactorily controlled and has been adequately validated with batches of the same size which have been used in clinical phase 3 trials and which are intended for commercial production. The approach for validation of the life-time (including performance and sanitation efficiency) of diafiltration and ultrafiltration filters used throughout the manufacturing of conjugates, are satisfactory described.

- Specifications

Appropriate specifications have been provided for the MenA-CRM, MenC-CRM, MenW-CRM and MenY-CRM Conjugates.

The stability protocol for purified polysaccharides comprises testing for molecular size distribution, O-acetyl content and dry weight. Real time stability data up to 36 months from clinical phase 3/process validation batches for MenA, W and Y PS support the proposed shelf-life of 36 months at ≤ -15°C for the

purified polysaccharides. Real time stability data up to 24 months from clinical phase 3/process validation batches for MenC support the proposed shelf-life of 30 months at $\leq -15^{\circ}\text{C}$ for MenC PS.

The average degree of polymerisation (aDP) is controlled at the level of sized oligosaccharides, but only for MenA and MenC oligosaccharides at the level of activated oligosaccharides. This was adequately justified. Furthermore, the activated oligosaccharides are stored as dry powders at $\leq -15^{\circ}\text{C}$, conditions likely not to affect the glycosidic linkage.

The characterisation aimed at both characterising the intermediates and drug substances and to verify physiochemical comparability between early clinical phase 3 batches manufactured at Siena and clinical phase 3/process validation batches manufactured at the Rosia site. In general, characterisation of the intermediates (CRM, polysaccharides, sized and activated oligosaccharides) are considered satisfactory and demonstrate physiochemical comparability between batches manufactured at the two sites. The characterisation of the drug substances on the other hand is not fully comparable. Siena batches contain additional polydispersion or higher levels of aggregates/ complexes than the Rosia batches, which is due to aggregation of a non-covalent nature. Slight variations in the conjugate purification conditions could affect the variable formation of this additional population of molecules. The agreed set of specifications (see above) for the drug substance is, however, considered sufficient to ensure consistency.

Most of the tests and specifications performed as part of the routine testing on the drug substances are in compliance with the Ph. Eur. monograph Meningococcal group C conjugate vaccine. A specification for bioburden and not sterility has been set for the drug substance bulk prior to storage even if this is a requirement according to the Ph. Eur. monograph for Meningococcal group C conjugate vaccine. However, the proposed limit for bioburden of the drug substance is considered acceptable in view of limits for bioburden already accepted for other (non-vaccine) biologicals. Microbiological quality of the Men CWY drug product is assured by additional measures.

Furthermore, based on the batch analysis data of Men conjugate bulks, the proposed specification limits for glycosylation grade (saccharide/protein ratio) and total saccharide are considered sufficiently justified.

Upon request the Applicant committed to reintroduce percentage of asymmetry and dispersion index as routine releasing testing for all four drug substances and setting appropriate limits. Finally, the company committed to establish a specification for appearance for the drug substance in accordance with the ICH Q6B.

With the exception of the in vivo test for immunogenicity, which has been abandoned after completion of the process validation, the analytical methods are in general considered adequate.

Additional information is provided concerning the container closure systems used. The equivalence of the cryotubes during the stability study and glass containers for routine storage of activated oligosaccharides is justified.

- Stability

The available stability up to 36 months data for drug substances support the proposed shelf-life of 36 months at $\leq -15^{\circ}\text{C}$. The protocol for the real-time stability is considered acceptable.

The available stability data for activated oligosaccharides for up to 24 months at $\leq -15^{\circ}\text{C}$ show no negative trends for the parameters tested (active ester group content, free N-hydroxysuccinimide, O-acetyl content and dry weight). A supposedly upward trend for free HNS has been clarified by the company. The applicant has satisfactorily justified that the current stability protocol for activated oligosaccharides, which

does not include monitoring of a DP or molecular size distribution, is sufficient to monitor stability of this intermediate.

Medicinal Product

Menveo consists of one vial containing the MenA lyophilized conjugate component (MenA Lyo) and one syringe containing the MenCWY liquid conjugate component (MenCWY Liquid). One dose of Menveo contains 10 µg of MenA saccharide, and 5 µg of each of the MenC, MenW and MenY saccharides, while the protein content ranges from 32.7 and 64.1 µg CRM₁₉₇ protein /dose. The excipients are sucrose and potassium dihydrogen phosphate from the MenA lyo component (12.5 mg and 5 mM, respectively) and sodium chloride, sodium dihydrogen phosphate monohydrate, and disodium phosphate dihydrate from the MenCWY liquid component (4.5 mg/ml, 2.5 mM, and 7.5 mM, respectively). The product is both preservative-free and non-adjuvanted. The MenCWY Liquid is a sterile, colorless, and clear solution for injection, supplied in single-dose 1.0 mL glass syringes (without needle) closed with halobutyl teflon coated rubber stoppers and a tip cap of butylic rubber formulation with latex. MenA Lyo is a sterile white to off-white cake, presented in a 2 mL glass vial with a halobutyl stopper. After reconstitution, the solution appears clear and colourless to slightly yellow.

- **Pharmaceutical Development**

The product development has been adequately described and the rationale for the final formulation justified.

- **Adventitious Agents**

The raw materials of ruminant or human origin are listed.

The Casamino Acids and the Q-Sepharose XL chromatography matrix both use bovine milk certified as being in compliance with the requirements of the EMEA's current Note for Guidance EMEA/410/01 and the FDA's 59 FR 44591 and 9 CFR 94. Neither human hair nor poultry feathers (used in the production of L-Cysteine Hydrochloride Monohydrate) are thought to be risks for transmission of TSE's. Moreover, from mid-2002 onwards, L-Cysteine Hydrochloride Monohydrate has been produced using raw materials of plant origin.

Viral clearance studies are considered not applicable.

- **Manufacture of the Product**

Manufacturing processes for the drug substances were transferred in Q3 2005 from Novartis Siena to Novartis Rosia and the process validation was conducted in 2006. All clinical batches of MenCWY Liquid have been formulated at the Rosia site, in 2 different buildings. All clinical batches of MenA Lyo have been formulated and freeze-dried at Novartis, Marburg.

The manufacture of MenCWY Liquid consists of the following steps:

- *Formulation*: Preparation of buffered saline solution in a mixing tank, dispensing of drug substances in the buffered saline solution and sterile filtration of the mixed solution through a 0.22 µm filter cartridge into the formulation vessel prior to storage for NMT 3 months at 2- 8°C .
- *Filling* of the MenCWY Liquid component in 1 mL syringes.

The manufacture of MenA Lyo consists of the following steps:

- *Formulation and Sterile Filtration*: Thawed MenA–CRM conjugate bulk is formulated in potassium phosphate buffer with sucrose, sterile filtered (0.22 µm) and filled the same day or stored at a temperature of 2-8°C for no longer than 24 hours. If formulation and filling are not performed in 24 hrs, then an additional sterile filtration step will be performed.
- *Filling and lyophilisation*: Sterile, depyrogenated vials are filled and lyophilised. The vials are stored at 2- 8°C until shipment from Marburg to Rosia at 2- 8°C.

The manufacturing processes are well described. It is confirmed that blending of batches or sub-batches of drug substance in the formulations is performed. The use of drug substance subjected to a second round of freezing and thawing was validated. However, the Company will only use MenW and MenY CRM conjugates subjected to a second freeze/thaw cycle until results from a MenC CRM freeze/thaw study are available.

The Drug Product manufacturing process for both the MenA lyo and MenCWY liquid product concerns a standard formulation/filling (lyophilisation) process. More information was requested on the validation of the used 0.2 µm filters as well as the proposed bioburden limits before filtration. The filtration procedure and type of filter is demonstrated to be satisfactory by means of a microbial challenge test using a suitable test micro-organism in accordance with Ph.Eur. 5.1.1. It is confirmed that pre and post filter integrity is tested.

With the company's commitment to initiate filling of the final container not later than 24 hours after completion of sterile filtration of the MenCWY bulk the company solves the main issue raised during the procedure.

All excipients used in the Menveo are compendial (Ph. Eur./USP). Minor issues were solved on request.

- Product Specifications

The panel of product specifications for release of the final lot vaccine comprises for MenCWY Liquid, tests for: Identity, total and free saccharide of MenC-CRM, MenW-CRM and MenY-CRM, appearance, volume, pH, osmolarity, endotoxin and sterility; and for MenA Lyo tests for: Identity, total and free saccharide, appearance, appearance after reconstitution, residual moisture, protein content (BCA), pH (after reconstitution), sucrose, endotoxin and sterility. The Applicant has provided batch analysis data of MenCWY Liquid and of MenA Lyo showing that the results on free saccharide are well below the current specification limit. Upon request the free saccharide % limits for release and stability have been aligned and tightened and are identical for the three glycoconjugates in MenWCY liquid. The proposed limit for free saccharide in MenA lyo is agreed. Limits for MenCWY endotoxin content were justified upon request. Compared to the Drug Substance, the saccharide content in the Drug Product(s) is significantly lower as it is diluted to the final dosage form. It was explained that based on the saccharide content the specification could not be set tighter. The explanation was satisfactory.

Satisfactory validation of the test methods have been provided. Regarding the test for total and free polysaccharides, the procedure for standard preparations and the limits of quantification were further clarified.

Protein content is only tested on MenA Lyo to demonstrate process consistency. The omission of a test for protein content for MenCWY Liquid is justified.

After successful process validation, Novartis decided to remove the tests for Pyrogen, Mouse Immunogenicity tests, MenA-, MenC-, MenW- and MenY-CRM ELISA and general safety/abnormal toxicity tests from the routine analytical testing of MenCWY Liquid and MenA Lyo. In addition, the High

performance Gel Permeation Chromatography (HPGPC) based tests for Hydrodynamic Size, Percentage of Asymmetry, and Dispersion Index for MenA Lyo were abandoned.

The Applicant has committed to reintroduce the HPGPC tests in the release testing as well as in the stability testing for MenA Lyo.

The container closure system has been adequately described for the MenA Lyo presentation. A satisfactory description of the syringe for MenCWY Liquid was provided upon request.

A container closure integrity test has been performed for syringes in order to demonstrate the suitability of container closure system. Apparently this validation was performed using an equivalent syringe to the syringe intended for use in commercial production. Information concerning the equivalence between the two syringes has not been provided, however the Company has initiated a new Container Closure Integrity Test (CCIT) on the syringe intended for use in commercial production.

- Stability of the Product

A shelf-life for MenCWY Liquid and MenA Lyo of 24 months when stored at 2 - 8°C has been accepted. The applicant commits to complete the stability study through to 48 months shelf-life for the process validation lots. Stability data for the process Men A and MenCWY validation lots data up to 18/24 months have been provided. Accelerated stability testing and supportive stability data from drug substances produced at Siena were already available. For MenCWY Liquid all the stability data are within the specification limits. All the stability data provided for MenA Lyo are within the specification limits and show no or little change in the total and free saccharide, pH, and residual moisture. On request the applicant has committed to re-introduce the percentage of asymmetry and dispersion index tests in all future stability studies for MenA Lyo Drug Product.

Due to the low performance of the immunogenicity assay, the highly variable immunogenicity data is not considered adequate for monitoring the stability of the drug product and the Applicant intends to cease performing the immunogenicity/ELISA testing for routine stability testing. This is in agreement with the Scientific advice given by EMEA.

The submitted stability data for the reconstituted vaccines support a shelf-life of 24 hours at both 2-8°C and 36-38°C.

In addition, the Applicant has also committed to submit data which support a 24 hrs shelf-life of the reconstituted vaccine with MenCWY Liquid and MenA Lyo components at or beyond their maximum shelf-life and committed to inform if any deviations are observed.

GMP compliance:

The GMP inspection to the Novartis Vaccines & Diagnostics S.r.l. site located in Localita Bellaria-Rosia (Sovicille, SI), Italy has been conducted from 20-25 September 2009 and 31 deviations were identified. Company's responses were received on 16 November, while the final GMP inspection report was issued on 3 December 2009. It is concluded that the activities required to fully solve all the points raised during the GMP inspection required time, however the site can be accepted manufacturing Menveo provided that: an interim report is provided not later than three months updating on the progress of the resolution of open deviations. A further inspection will be carried out with a timeline for reporting by September 30th, 2010.

Regarding the use of batches produced prior to the inspection:

All batches manufactured were produced in a GMP licensed facility. The inspection revealed major but not critical concerns. Based on this it is considered that the batches produced (in 2007-2008/9), prior to the full implementation of changes to deal with the bioburden problems can be used provided that they met the specifications (in place at the time). The bioburden levels at intermediate steps for the 2007-2008/9 batches and incomplete inactivation of *N. meningitidis* group W at the inactivation step, are no reason for concern, because subsequent steps have a sufficient inactivation and removal capacity.

2.3 Non-clinical aspects

Introduction

The non-clinical program of studies with MenACWY consists of three non-GLP immunogenicity studies in mice and three completed GLP toxicology studies in rabbits. The results of two GLP repeat-dose toxicity studies in rabbits (Study 489062 and AA78333) testing the current formulation of MenACWY (non adjuvanted) were also submitted during the procedure.

Pharmacology

- Primary pharmacodynamics

Immunogenicity in mice and rabbits has been investigated by using an ELISA to measure antibodies against each serogroup and serum bactericidal assay (SBA) measuring functional antibodies for each serogroup.

Immunogenicity studies in mice

Mice were treated twice by subcutaneous (SC) injection, 4 weeks apart, with MenA-CRM, MenC-CRM, MenW-CRM and MenY-CRM. Sera were collected 14 days after the second dose and analysed for antibody levels (ELISA) and functionality (SBA). In these studies, the antigens were formulated individually or in combination, with different antigen ratios, with or without either Al(OH)₃ or AlPO₄ adjuvant, and with increasing adjuvant dosages.

Immunogenicity study in mice with adjuvanted, Al(OH)₃ or AlPO₄, tetravalent combinations of MenA, MenC, MenW and MenY conjugates - Study 243/07

The aim of this study was to compare the immunological response of mice treated with the four conjugated meningococcal oligosaccharides MenA, MenC, MenW and MenY, formulated with Al(OH)₃ or AlPO₄ adjuvants, at different antigen molar ratios.

Combinations of the four CRM-conjugates, adjuvanted with AlPO₄, were administered at the following antigen ratios of A:C:W:Y (weight:weight in µg of oligosaccharides): (4 or 2):2:2:2; (4 or 2):2:1:1; (4 or 2):2:0.5:1; (4 or 2):2:2:1; (4 or 2):2:1:0.5; or (4 or 2):2:1:2.

The combination adjuvanted with Al(OH)₃ was administered at the ratio of (4 or 2):2:2:2.

The ELISA GMT values showed differences between the antigens in their interaction with the adjuvants/other antigens. E.g. with MenW, the titres tend to be lower with AlPO₄, whereas for MenY the titres tend to be lower with Al(OH)₃. Whether there is or there is no interference between antigens can hardly be concluded because of all the other differences between the treatments.

As the intended formulation does not contain any adjuvant, these data are of limited value, and cannot be used to predict the optimal ratio between the antigens.

Immunogenicity study in mice with adjuvanted, Al(OH)₃ or AlPO₄, monovalent and tetravalent combinations of MenACWY conjugates - Study 244/07

Immune responses were evaluated in mice using antigens combined at ratios of 1:1:1:1 (at 2 µg of each oligosaccharide) or 1:1:0.25:0.5 (at 2 µg of A and C, 0.5 µg of W, and 1 µg of Y oligosaccharides) versus single antigens. The rationale for the combinations with lower MenW-CRM and MenY-CRM oligosaccharide concentrations was to address potential antigen interference with Al(OH)₃- or AlPO₄-containing formulations, especially with respect to the MenA component.

ELISA and SBA titres showed immune responses and functional activity in mice with all formulations tested. Overall, no notable differences in antibody responses were observed when antigens were combined. Immunogenicity of MenC-CRM, MenW-CRM and MenY-CRM did not change when the conjugates were administered alone or in combination. However, for the MenA conjugate two of the six tetravalent formulations did not induce bactericidal antibodies.

In all treatment groups alum adjuvants were included. The absence of interference is an optimistic conclusion as in fact the confidence intervals are wide. As the intended formulation does not contain any adjuvant, these data are of limited value, not having any predictive value for the human situation.

Immunogenicity study in mice of tetravalent conjugated MenACWY vaccine with different adjuvant dosages and without adjuvant - Study 245/07

This study investigated the immune responses of mice given the tetravalent combination of MenACWY without adjuvant or formulated with increasing doses of AlPO₄ adjuvant. The dose volume of 0.5 mL contained 2 µg of each oligosaccharide. When used, the AlPO₄ adjuvant dosages tested were 0.060, 0.030 or 0.015 mg (of Al³⁺ per dose).

ELISA and SBA titres showed immune responses to all antigens with all formulations tested. No major difference were observed with the various aluminium phosphate dosages or in the absence of adjuvant, but the best immune response to MenA-CRM antigen was obtained with the formulation containing 0.06 mg Al³⁺, and somewhat lower responses were observed with the lower adjuvant concentrations or without adjuvant.

The positive influence of AlPO₄ on the titre measured by ELISA as well as by SBA is in contrast to the finding of the study mentioned above, where this adjuvant was negatively associated with the immune response. It is the only mouse study in which a group without adjuvant has been tested, but no conclusion is possible from this single experiment. This study does not contribute to the proof-of-concept.

Immunogenicity studies in rabbits

As part of toxicity studies in rabbits, serum samples were collected to confirm the immunological response of MenACWY in the experiment. Antibody assays (ELISA and SBA) were not conducted under GLP.

Single/repeated dose toxicity - Study 02-2752

The general toxicology study with alum-adjuvanted MenACWY formulations was designed with a single-dose and a repeat-dose aspect (5 doses each administered 2 weeks apart). The rabbits received intramuscularly 40µg saccharide/dose containing all four antigens at a concentration of 10 µg each.

Sera from controls were negative for antibodies throughout the study. After a single dose, antibody responses were detectable (ELISA and SBA) 14 days after injection in all animals given the MenACWY+Al(OH)₃, while fewer than half of the animals given the AlPO₄ formulation had seroconverted. In the repeat-dose aspect of the study, antibody titres (ELISA) and function (SBA) were highest after the third dose and declined thereafter, but were still detectable 14 days after the last injection. A non-adjuvanted formulation was not tested in this study.

Dose-range finding Developmental and reproductive toxicity (DART) - Study UBA00020

Two groups of animals receiving MenACWY and MenACWY+AlPO₄ respectively (0.5 ml containing 10 μ of Men A, 5 μ each of Men C, W and Y) were used only for blood sampling for antibody analysis. Five intramuscular injections were administered to 5 female rabbits/group (for the dosing scheme, see Toxicology section). Blood samples were collected from these animals during the pre-mating phase on days 3, 17 and 31 (approximately 48 hours post-injection) and during gestation on days 7 (prior to dosing) and 29 (at Caesarean section). Fetal blood was also collected and pooled on gestation day 29.

The ELISA results demonstrated that the titers were approximately 2 times higher with MenACWY containing AlPO₄ adjuvant than without adjuvant and that fetal sera contained high specific titers against all serogroups. The bactericidal antibody results also demonstrated that responses to the adjuvanted MenACWY were higher than to non-adjuvanted vaccine. Bactericidal titers were about the same level in maternal sera as in the fetal sera.

Pivotal DART study - Study UBA00038

One hundred and eight New Zealand White female rabbits were randomly assigned to four dosage groups. Group II and IV rabbits were administered intramuscular injections of MenACWY (without adjuvant, similar to final product) and Group I and III rabbits were administered intramuscular injections of the control article (0.9% Sodium Chloride Injection). Five intramuscular injections were administered to 27 female rabbits/group (for the dosing scheme, see Toxicology section). Antibody analysis and serum bactericidal activity were performed on maternal and fetal/pup blood samples to confirm exposure.

The ELISA titers peaked around day 7 to 20 of gestation and declined after that. The titers for MenW and MenY at day 29 of lactation were similar to pre-study titers. On gestation day 29 the fetal sera titers were higher than the corresponding maternal titers. Bactericidal titers at gestation day 29 were higher against MenA and MenC than against MenW and MenY. The bactericidal titers in fetal sera were similar or higher than the corresponding maternal titer.

In the two reproductive/developmental (DART) toxicity studies described above, the current (non-adjuvanted) formulation of MenACWY was tested. The vaccine was immunogenic in maternal rabbits (does) and antibodies were detectable (ELISA) and functional (SBA) in fetuses on day 29 of gestation. F1 offspring had ELISA titres that were comparable to their does on day 29 of lactation.

The immunogenicity data from the dose-range finding DART study as well as from the pivotal DART study in rabbits clearly indicate an immune response to the individual antigens. It cannot be concluded whether the vaccine, although inducing serum-bactericidal activity, will induce protection in these rabbits. The non-adjuvanted vaccine clearly results in a higher MenA response than the alum-adjuvanted responses, indicating that indeed the mouse data are of limited value in this respect.

The data from pups (after caesarian section and Lactation day 29) indicate the placental transfer of IgG during the latter part of pregnancy and transfer via milk. It shows that it might be possible to vaccinate pregnant mothers to protect their children, although the clinical relevance of the titre reported on Lactation Day 29 is not known.

- Secondary pharmacodynamics

No studies investigating secondary pharmacology were performed with MenACWY based on the nature of the product and the existing nonclinical safety/tolerability profile. The drug substances in MenACWY consist of purified oligosaccharides conjugated to CRM197, and the non-active constituents of the vaccine are well-established ingredients of pharmaceutical preparations.

In some repeated dose toxicity studies heart rate has been recorded. However, these recordings were made at the 5th day after the 2nd injection and at the 6th day after the 3rd injection. No effects have been observed. The choice of these time points to measure heart rate is without any rationale and was not explained by the

applicant. In the last study performed in rabbits and requested by the EMEA, heart rate has been measured 2 hours after the first and after the second injection. No effects have been recorded. Monitoring each day during at least a few days after administration would have been a better option.

- Safety pharmacology programme

No studies investigating safety pharmacology were performed with MenACWY based on the nature of the product and the existing nonclinical safety/tolerability profile.

- Pharmacodynamic drug interactions

No studies investigating pharmacodynamic drug-drug interactions were performed with MenACWY based on the nature of the product and the existing nonclinical safety/tolerability profile.

Pharmacokinetics

Pharmacokinetic testing is not required for vaccines.

Toxicology

The MenACWY toxicology program consists of a completed GLP general toxicology study in rabbits with single- and repeat-dose aspects (study 02-2752), two GLP general toxicology studies in rabbits with two doses (studies AA78333 and 489062) and pilot and definitive rabbit reproductive and developmental toxicity studies (DART studies).

All studies were performed in rabbits using 1-2× the clinical dose and the clinical route of administration. These studies addressed the potential for local and systemic toxicity in males and nulliparous females (single/repeat-dose toxicity), and potential for effects on pregnant females, their fetuses, and F1 offspring (reproductive and developmental toxicity).

The number of vaccine doses administered to rabbits in these studies exceeded the intended number proposed for immunization of adolescents or adults by up to four doses. On a body weight basis, each dose to a rabbit was equivalent to approximately 10 times the dose administered to an adolescent (using 40 kg for human subject and 4 kg for rabbit).

Comparable manufacturing processes have been used throughout the development of the vaccine so any impurities or residuals would have been tested in the repeat-dose and reproductive and developmental toxicity studies in rabbits. The drug substances (MenA-CRM, MenC-CRM, MenW-CRM, and MenY-CRM), and any manufacturing impurities, were tested regardless of the presence of aluminium-based adjuvants.

- Single dose toxicity (Study 02-2752)

In the single-dose aspect of study 02-2752, rabbits (4/sex/group) received a single intramuscular injection of 40µg total oligosaccharides. Antigens were formulated with either aluminium phosphate or aluminium hydroxide adjuvant. One control group received aluminium phosphate and a second control group received aluminium hydroxide adjuvant. Two animals/sex/group were necropsied 2 or 14 days post-dose. The study parameters evaluated were as follows: viability checks twice a day, clinical signs daily, physical examinations twice a day, dermal scoring of injection sites performed 1 and 2 days after each treatment, body weights weekly and food consumption recorded daily. Body temperatures were measured before and 2 days after injection or weekly during non-dosing periods. Heart rates were measured pre-test and on days 21 and 50, clinical pathology analyses (hematology, serum chemistry, and coagulation, including fibrinogen) were performed pre-test, 2 days after each treatment and at recovery necropsy.

No specific effects have been observed in the single dose part of the study.

- Repeat dose toxicity

Study 02-2752

In the repeat-dose aspect of study 02-2752, rabbits received five intramuscular injections of 40 µg total oligosaccharides. The study parameters evaluated were the same as described above for the single-dose aspect with the addition of ophthalmoscopic examinations performed pre-test and before each necropsy. Rabbits were necropsied 2 or 14 days post-last dose (days 58 or 70, respectively). There was no systemic toxicity associated with adjuvanted MenACWY given two weeks apart. Reversible decrease in white blood cell counts and transient increases in fibrinogen occurred in treated animals; fluctuating cell counts are consistent with the administration of immunologically active materials in animals and men and fibrinogen elevation may be indirectly mediated by circulating cytokines and are among the transient abnormalities commonly associated with activation of the immune system. Partially-to-fully reversible, generally minimal to slight, injection site reactions were present in all study groups, with a slightly higher incidence and/or severity in animals receiving the MenACWY formulations.

Combining the single and repeat dose toxicity studies in a single study design is a rational approach saving animals. The choice of time points to measure body temperature and heart rate was insufficiently justified and was not focused to detect effects of the vaccine.

Results from the two other 2-dose toxicology studies in rabbits with non-adjuvanted MenACWY provided additional nonclinical support for the product and confirmed the toxicological profile of the vaccine.

Study AA78333

New Zealand White rabbits (8/sex) were assigned to 2 groups. Necropsies (4/sex/group) were on study days 16 (main) and 28 (recovery). Two intramuscular injections of 25 µg of non-adjuvanted MenACWY administered 2 weeks apart were locally and systemically well tolerated in rabbits. Body temperatures were measured before and 2 hours after each injection and no relevant effects were observed. Occasional and slight and transient skin redness or swelling seen in both group animals correlated with minimal/slight dermal or intramuscular inflammation and hemorrhage at microscopic examination. These changes were of similar nature and severity in treated and control groups and were therefore considered to be a consequence of the intramuscular injection procedure. There were no findings in this study that changed the non clinical safety profile of the vaccine that had been established with adjuvanted formulations.

The dosing regimen used in this study (2 doses given 2 weeks apart) exceeded the planned clinical regimen for adolescents (> 11 years of age) and adults by 1 dose. Each dose was equal to the proposed clinical dose of 25 µg total oligosaccharides and CRM₁₉₇. On a microgram per kilogram basis, rabbits (approximately 4 kg) received ~10 times the dose to an adolescent, assuming a 40 kg human body weight.

Study 489062

In study 489062 repeat-dose toxicity and local tolerability of MenACWY were evaluated. New Zealand White rabbits were assigned to 2 groups and received intramuscular injections of MenACWY or saline solution (control article). Dose and route of administration were the same as above (study AA78333). Several animals of both groups developed symptoms consistent with 'enteritis complex' (including mucoid enteropathy) and died or were euthanized in extremis. Toxicological evaluations were based on surviving animals only, resulting on a low number of animals in the control groups.

The following parameters were evaluated in surviving animals: viability checks (twice a day), clinical signs (daily), skin observations of injection sites (1 and 2 days after each treatment and daily up to resolution of any finding), body weights (weekly) and food consumption (twice a week). Body temperatures were measured before dosing and 2 and 24 hours after each injection. Ophthalmoscopic examination was performed pre-test and before each necropsy, heart rate and respiratory rate were measured pre-test, prior of dosing and 2 hours after each dose on Days 1 and 15, clinical pathology analyses (hematology, serum chemistry, and coagulation, including fibrinogen) were done pre-test, 2 days after each treatment (Days 3 and 17) and at recovery necropsy. Immunogenicity was assessed during the study by ELISA and SBA. Organ weights (adrenals, brain, heart, kidneys, liver, lungs, ovaries, spleen, testes and thymus) and macroscopic examinations were performed. The complete WHO tissue list was collected and evaluated histopathologically in this study. This study was initially required as additional study by the EMEA.

There was no systemic or local toxicity associated with two 0.5 mL intramuscular injections of 25 µg of non-adjuvanted MenACWY given two weeks apart. An immune response was apparent after the 2nd dose while low or no antibodies were detected after the 1st dose. Due to the 'enteritis complex' occurring during the study, Novartis chose to initiate a second study (Study AA78333, described above).

- Genotoxicity

No studies investigating genotoxicity were warranted based on the nature of the product and/or the existing non clinical and clinical safety/tolerability profiles, which is acceptable.

- Carcinogenicity

No studies investigating carcinogenicity were warranted based on the nature of the product and/or the existing non clinical and clinical safety/tolerability profiles, which is acceptable.

- Reproduction Toxicity

Reproductive and developmental toxicity was evaluated in New Zealand White rabbits. This species has demonstrated sensitivity to developmental toxicants, historical data are available, and antibodies are elicited by treatment with MenACWY in this animal model. A GLP dose-ranging study (non-pivotal) and a pivotal GLP study were conducted. These studies were designed to evaluate ICH Guideline S5 (R2) stages A through E (with the exception of effects on male fertility and the oestrus cycle) and to comply with FDA guidance (Considerations for Developmental Toxicity Studies for Preventative and Therapeutic Vaccines for Infectious Disease Indications).

The studies were designed to have a maximum stimulation of the antibody concentration (mentioned as exposure) in order to ensure maximum exposure of the fetus to the antibodies. However, this is unlikely to occur in animal studies, as there is no placental transfer of IgM antibodies during the whole pregnancy, and placental transfer of IgG only in the second half of the pregnancy.

Dose-range finding Developmental and reproductive toxicity (DART) - Study UBA00020

In study UBA00020 the potential effects of MenACWY (either adjuvanted with AlPO₄ or without adjuvant) on maternal and fetal parameters were evaluated. Five intramuscular injections were administered to 5 female rabbits/group every other week: 3 times before mating at 1× the clinical dose of 25 µg and two times during gestation at 1× or 2× the clinical dose (25 µg or 50 µg respectively).

Pre-mating dosing was on days 1, 15, and 29 to elicit high titres at the time of mating and early in gestation. The treatment on gestation days 7 and 20, at either 25 or 50 µg, was intended to maintain antibody levels and to test the potential for maternal or fetal toxicity or teratogenicity. Dosing during

gestation ensured fetal exposure to the vaccine components and allowed the determination of fetal exposure to maternal antibodies via placental transfer, which was expected based on data in pregnant mice (Richter 2004). On day 29 of gestation, Caesarean sections were performed.

There were no deaths or maternal treatment-related findings in this study with the exception of a reduction of weight gain (61.9% of the control group) in rabbits given the 50 µg adjuvanted dose during gestation. No Caesarean section or litter parameters were affected in any group by treatment.

Pivotal DART study - Study UBA00038

The objective of this pivotal study was to assess the potential effects of MenACWY on reproductive and developmental toxicity in female rabbits and their fetuses or F1 offspring.

The potential toxicity of MenACWY was assessed in females before cohabitation, through mating with untreated males, and during gestation and lactation. This study was designed to evaluate ICH Harmonised Tripartite Guideline stages A through E of the reproductive process (with the exception of determination of effects on male fertility and the oestrus cycle) and would detect any effects on tubal transport, implantation, gestation, parturition, lactation, and maternal behaviour in female rabbits, and development of the offspring of the treated females. The F1 generation was observed for 4 weeks to detect the manifestation of any delayed effect.

Intramuscular doses (0.5 mL) were administered to alternate hind limbs. Three doses were administered prior to gestation to ensure induction of high antibody levels. Two doses were administered during gestation to expose fetuses to the vaccine and to maintain antibody titres.

MenACWY was well tolerated and there were no treatment-related maternal effects, no embryofetal toxicity was observed, and there were no developmental effects in F1 offspring during 4 weeks of post-natal observation. Based on the study results, MenACWY was not a reproductive or developmental toxicant in rabbits.

- **Local tolerance**

The pivotal single and repeat-dose intramuscular study in rabbits (Study 02-2752) included a full evaluation of local tolerability. Microscopic observations following repeated dosing included minor inflammatory and degenerative changes at the injection sites, with slightly greater severity and/or incidence in vaccine-treated animals compared to control groups. In most cases the findings were graded as minimal or slight in severity. Occasional focal haemorrhage in the dermis, subcutaneous tissues, or in the underlying muscle layers was noted in all groups. These changes correlated with discoloration seen at macroscopic examinations. The incidence and severity of findings was decreased following the 14-day recovery period.

Data from the two additional repeat-dose toxicity studies (489062 and AA78333) has also been submitted and no local or systemic toxicity related to the vaccine was observed. The studies conducted by the company confirm the safety and tolerability of the vaccine.

Ecotoxicity/environmental risk assessment

In accordance with EMEA "Guideline on the Environmental Risk Assessment of medicinal products for human use" (EMEA/CHMP/SWP/4447/00) which specifies that vaccines are exempt due to the nature of their constituents, no additional information has been performed.

Discussion on the non-clinical aspects

There is no well-accepted animal challenge model in which to study protection from disease caused by *N.meningitidis* strains A, C, W and Y post-vaccination. Therefore, non clinical pharmacology studies have focused on demonstrating the immunogenicity of the vaccine and on showing that the elicited serum antibodies can kill bacteria of the homologous strains.

The Serum Bactericidal Activity (SBA) assay is internationally recognised as the most important method for measuring functional activity of antibodies elicited after meningococcal polysaccharide-based vaccines. SBA was established as correlate of protection for polysaccharide vaccines in 1969. The vaccine or its components have not been tested in any animal model of disease. Although limitations exist it would have been important to gain experience. However, if the proof-of-concept is proven in clinical studies than no further animal studies are needed.

General safety/abnormal toxicity testing of each clinical lot has been performed in mice and Guinea pigs (USP and Ph.Eur.). These studies, together with the biochemical/biophysical release tests, ensure the acceptability of individual clinical or commercial lots. There were no manufacturing impurities or residuals at levels that constitute any cause for concern.

The general safety/abnormal toxicity testing in mice and guinea pigs are of limited value from a non clinical point of view and can be discarded from future procedures.

The results of the GLP general toxicology study in rabbits with single and five repeated doses support the safety and immunogenicity of MenACWY.

The proposed indication for this dossier is for the administration of 1 dose of MenACWY to individuals from 11 years of age. The non clinical immunogenicity and toxicology data, in combination with the clinical data, support the safety and immunogenicity of MenACWY. Theoretical safety concerns with respect to the use of MenACWY in humans, such as potential hypersensitivity reactions to vaccine ingredients and interactions with ongoing therapy that could diminish antibody responses to active immunization, have been addressed in the label.

2.4 Clinical aspects

Introduction

The clinical development program of the MenACWY conjugate vaccine included early studies (V59P1 & V59P3 (preliminary), and V59P2, V59P4, and V59P7) designed to investigate the effect of different doses of each serogroup antigen (A,C,W,Y) on the immune response and the need for an adjuvant in the formulation.

The safety and immunogenicity of the final non-adjuvanted 10-5-5-5 MenACWY formulation was evaluated in individuals aged 11 years and older in a series of phase 2 and 3 studies: V59P6, V59P11, V59P13, V59P17, and V59P18. The study design and main objectives of the studies are described in Table 1 below.

In addition to the submitted studies supporting the chosen formulation (i.e. dose & adjuvant) and the immunogenicity and safety in the proposed indication, the applicant has submitted some studies conducted in toddlers and children under the age of 11 years old which fall outside the proposed indication. Lastly, four more studies have been planned in children under the age of 10 (V59P5E1, V59P20, V59P21 & V59P22).

Within the clinical development programme, no clinical efficacy studies were undertaken, only immunogenicity was assessed. Control vaccines used in the above mentioned studies included vaccines containing polysaccharides of serogroups A, C, W, and Y (Menactra™, Sanofi Aventis; Menomune™, Aventis Pasteur); Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed (Tdap: Boostrix™ [EU formulation in V59P11 and US formulation in V59P18]); and Human Papilloma Virus (HPV) vaccine (Gardasil™, Merck).

Scientific advice regarding the clinical development programme was sought on several occasions from the UK regulatory authority and the CHMP. The following essential issues were put forward in the initial scientific advice by the CHMP:

- The use of human complement in the Serum Bactericidal Assay (SBA) was endorsed
- Detection of SBA against each of the polysaccharide antigens in titres of $\geq 1:4$ is a confident measure for clinical protection
- The use of a more conservative hSBA threshold titre of 1:8 for the demonstration of non-inferiority is acceptable
- It is more appropriate to make a distinction between initially seropositive and seronegative persons; a fourfold rise in hSBA titres should be considered as primary endpoint for initially seropositive persons – hSBA titre of $\geq 1:8$ one month after vaccination should be considered as primary endpoint for initially seronegative persons only
- The suggested comparator vaccine (*Menactra in adolescents >11 years*) is adequate in principle.
- Additional immunological aspects covered in WHO recommendations for MenA and MenC vaccines should be considered (persistence of antibodies, response to carrier protein, etc)
- Standardization of the SBA should be extensively discussed
- Due to low incidence rates of MenACWY disease it is considered not feasible to generate clinical efficacy data; a plan should be in place to evaluate effectiveness post licensing.

Largely, the Applicant followed the scientific advice as provided by the CHMP. It should be noted however that in the Scientific Advice the company indicated that initial MA would be sought for children age 2 and older, and not 11 and older as is currently the case. The follow up scientific advice pertained to the clinical development in children younger than 10 years, and is not considered relevant to the current submission. Secondly, the standardisation of the SBA was not adequately discussed.

The following CHMP guidelines in particular are applicable for this application:

- Note for Guidance on the “Clinical Evaluation of New Vaccines” (EMEA/CHMP/VWP/164653/2005)
- Note for Guidance on “Statistical Principles for Clinical Trials” (CPMP/ICH/363/96)
- Note for Guidance on “Choice of a Non-Inferiority Margin” (CPMP/EWP/2158/99)

Table 1 Overview of submitted and ongoing clinical studies in the Menveo development programme, including study details

Study ID	Geographic Location	Study Objective (Primary)	Design	Test Product(s); Dosage Regimen; Route of Administration	Subjects by arm	Age groups included	No. of study centres
STUDIES FOR PROPOSED INDICATION:							
V59P6	US	Safety and Immune Response of One Dose MenACWY vs. Menomune®	Single-Blind, Randomised, Active Controlled Phase 2 Multi-Centre (2 stages)	<ul style="list-style-type: none"> • MenACWY 10-5-5-5µg Ad+ IM • MenACWY 10-5-5-5µg Ad - IM • Menomune® SC 	<ul style="list-style-type: none"> • 164 • 151 • 209 	11-17 y	3
V59P11	Italy	Safety and Immune Response of MenACWY with and without Boostrix®, vs. Boostrix® alone	Observer-Blind, Random, Controlled Phase 3, Multi-Centre	<ul style="list-style-type: none"> • MenACWY10-5-5-5 µg Ad- IM (+ Boostrix® [EU Formulation]) • MenACWY10-5-5-5 µg Ad- (+ Saline) IM • Boostrix® [EU Formulation] IM (+ Saline) 	<ul style="list-style-type: none"> • 359 • 357 • 353 	11-18y / 19- 25 y	14
V59P13	US	Lot to Lot Consistency of 3 Lots of MenACWY & Safety & Immune Response of MenACWY vs. Menactra™	Observer-Blind, Random, Controlled Phase 3, Multi-Centre	<ul style="list-style-type: none"> • MenACWY10-5-5-5 µg Ad- IM • Menactra™ IM 	<ul style="list-style-type: none"> • 2649 • 875 	11-18 y / 19- 55 y	44
V59P17	Argentina Colombia	Safety & Immune Response of MenACWY vs. Menomune® or Menactra™	Observer-Blind, Random, Controlled Phase 3, Multi-Centre	<ul style="list-style-type: none"> • MenACWY10-5-5-5 µg Ad- IM • Menactra™ IM • Menomune® SC 	<ul style="list-style-type: none"> • 1817 • 899 • 109 	19-55 y vs Menactra™ 56-65 y vs Menomune®	3
V59P18 <i>ongoing</i>	Costa Rica	Safety & Immune Response of MenACWY & without Boostrix® & Gardasil®	Open-Label, Randomized, Active Controlled Phase 3, Single-Centre	<ul style="list-style-type: none"> • MenACWY10-5-5-5 µg Ad- IM (co-administered with Boostrix®+ Gardasil®) • MenACWY10-5-5-5 µg Ad- IM followed by Boostrix® followed by Gardasil® • Boostrix® followed by MenACWY 10-5-5-5 µg Ad- IM followed by Gardasil® 	<ul style="list-style-type: none"> • 540 • 541 • 539 	Adolescents 11-18 y	1

Table 1. continued

Study ID	Geographic Location	Study Objective (Primary)	Design	Test Product(s); Dosage Regimen; Route of Administration	Subjects by arm	Age groups included
OTHER STUDIES INCLUDED IN SUBMISSION:						
V59P1	Switzerland	Safety & Immunogenicity Comparison of Two MenACWY Formulations vs. Mencevax®	Open Label, Randomized, Active Controlled, Phase 1, Single-Centre	<ul style="list-style-type: none"> • MenACWY10-10-10-10µg Ad+ IM • MenA+CWY 10-10-10-10µg Ad+ IM • Mencevax® SC 	<ul style="list-style-type: none"> • 30 • 30 • 30 	Adults 18-45 y
V59P1E1	Switzerland	Safety & Immunogenicity Persistence of Antibodies & Memory Response of Subjects Previously Vaccinated with either MenACWY or Mencevax®	Open Label, Active Controlled, Phase 2, Single-Centre	<ul style="list-style-type: none"> • 1/10th dose Mencevax® IM 	<ul style="list-style-type: none"> • 29 Total • 15 prior MenACWY • 14 prior Mencevax® 	18-45 y Previous participants in V59P1
V59P2	Finland Germany	Safety & Immunogenicity Dose Ranging Study	Observer-Blind, Randomized, Active Controlled, Phase 2, Multi-Centre	<ul style="list-style-type: none"> • MenACWY 10-10-10-10µg Ad+ IM • MenACWY 0-10-10-10 µg Ad+ IM • MenACWY 10-5-5-5 µg Ad+ IM • MenACWY 5-5-5-5 µg Ad+ IM • MenACWY 2.5-2.5-2.5-2.5µg Ad+ IM • Menjugate® IM 	<ul style="list-style-type: none"> • 109 • 106 • 103 • 101 • 104 • 97 	Toddlers (12-16 months)
V59P3	Switzerland	Safety & Immune Response of MenACWY with and without Adjuvant vs. Mencevax®	Observer Blind, Randomized, Active Controlled Phase 1 Single-Centre	<ul style="list-style-type: none"> • MenACWY10-10-10-10 µg Ad+ IM • MenACWY10-10-10-10µg Ad- IM • Mencevax® IM 	<ul style="list-style-type: none"> • 30 • 30 • 30 	Adults (18-45 years)
V59P4	US	Safety & Immunogenicity Dose Ranging; Men ACWY with & without Adjuvant vs. Menomune®	Double-Blind, Randomized, Active Controlled Phase 2 Multi-Centre	<ul style="list-style-type: none"> • MenACWY10-10-10-10µg Ad- IM • MenACWY5-5-5-5µg Ad-IM • MenACWY5-5-5-5 µg Ad+ IM • Menomune® SC 	<ul style="list-style-type: none"> • 81 • 79 • 75 • 80 	Toddlers (12-16months); MenACWY Children (3-5 years); Menomune®
V59P5	UK Canada	Safety & Immunogenicity Schedule Finding Two or Three Doses With Concomitant Infant Routine Vaccinations Persistence of Antibodies, Booster and Memory Response	Open-label, Randomized, Active Controlled Phase 2 Multi-Centre	<ul style="list-style-type: none"> • MenACWY+ & MenACWY+ Boost IM • MenACWY+ & no Boost IM • MenACWY+ followed by 1/5th Dose Menomune® SC • MenACWY- & 10-5-5-5 µg Ad- Boost IM • MenACWY- followed by 1/5th Dose Menomune® SC • Menjugate® & MenACWY+ Boost IM 	<ul style="list-style-type: none"> • 229 • 49 • 98 • 135 • 45 • 45 	Infants (2 months)

Table 1. *continued*

Study ID	Geographic Location	Study Objective (Primary)	Design	Test Product(s); Dosage Regimen; Route of Administration	Subjects by arm	Age groups included
OTHER STUDIES INCLUDED IN SUBMISSION: (Continued)						
V59P7	Finland Poland	Safety & Immune Response of MenACWY with and without Adjuvant vs. Mencevax®	Observer Blind, Randomized, Active Controlled Phase 2 Multi-Centre	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • 205 • 331 • 81 	Toddlers (12-35 months) Children (36-59 months)
V59P8	US	Safety & Immune Response of MenACWY vs. Menomune®	Single-Blind, Randomized, Active Controlled in Children Open-Label in Toddlers Phase 2 Single-Centre	<ul style="list-style-type: none"> • MenACWY • MenACWY (+PnC) • MenACWY (+DTaP) • Menomune® SC 	<ul style="list-style-type: none"> • 453 • 71 • 73 • 310 	Children (2-10 years) Toddlers (12-23 months)
V59P9	Canada	Schedule Finding Safety & Immune Response After One or Two Doses of MenACWY	Open Label, Partially Randomized, Active Controlled Phase 2 Multi-Centre	<ul style="list-style-type: none"> • MenACWY • Menjugate® followed by MenACWY 	<ul style="list-style-type: none"> • 125 • 50 	Infants (6 -12 months)
V59P10	Argentina	Safety & Immune Response of One Dose MenACWY vs. Menomune®	Observer-Blind, Randomized, Active Controlled Phase 3 Multi-Centre	<ul style="list-style-type: none"> • MenACWY • Menomune® SC 	<ul style="list-style-type: none"> • 950 • 550 	Children (2-10 years)

Table 1. *continued*

Study ID	Geographic Location	Study Objective (Primary)	Design	Test Product(s); Dosage Regimen; Route of Administration	Subjects by arm	Age groups included
OTHER COMPLETED OR ONGOING STUDIES OF MenACWY OUTSIDE OF INDICATION, NOT INCLUDED IN DOSSIER						
V59P2E1	Finland	Safety & Immune Response Following One Dose of Mencevax® 6 Months After One Dose of MenACWY	Open-Label, Active Controlled Phase 2 Single-Centre	Mencevax® SC	<ul style="list-style-type: none"> • 94 Prior MenACWY • 25 Naïve Subjects 	Toddlers (22-24 months)
V59P2E2	Finland	Safety & Immune Response Following One Dose of Mencevax® 12 Months After One Or Two Doses of MenACWY	Open-Label, Active Controlled Phase 2 Single-Centre	Mencevax® SC	<ul style="list-style-type: none"> • 175 Prior MenACWY • 62 Naïve subjects 	Toddlers (24-28 months)
V59P14	US Argentina Colombia	Safety & Immune Response of MenACWY given with US Routine Infant Vaccines Followed by MenACWY Booster vs. Routine Infant Vaccines Alone Followed by two Doses MenACWY in 2nd Year of Life	Open-Label, Randomized, Phase 3 Multi-Centre	<ul style="list-style-type: none"> • MenACWY (+ Routine Vaccines) • Routine Vaccines Only Followed by MenACWY 	<ul style="list-style-type: none"> • 3000 (planned) • 1500 (planned) 	Infants (2 months)
V59P16 Non-IND Study	UK	Safety & Immunogenicity Memory B Cell Response to MenACWY at 2, 4 and months of age	Open-Label, Randomized Phase 2 Single-Centre	• MenACWY	• 216	Infants (2 months)

Table 1. continued

Study ID	Geographic Location	Study Objective (Primary)	Design	Test Product(s); Dosage Regimen;	Subjects by arm	Age groups included
PLANNED STUDIES						
V59P5E1	UK Canada	Safety & Immunogenicity Persistence of Antibody Response in Children Previously Vaccinated with MenACWY as Infants	Open-label, Active Controlled Phase 2 \Multi-Centre	N/A	<ul style="list-style-type: none"> • 376 Planned Subjects (40 months) • 260 Planned Subjects (60 months) • 100 Planned Naïve Subjects 	Children 40 & 60m who previously participated in V59P5
V59P20	US Canada	Safety & Immune Response of MenACWY vs. Menactra™	Observer-Blind, Randomized, Active Controlled Phase 3 Multi-Centre	<ul style="list-style-type: none"> • MenACWY • Menactra™ 	<ul style="list-style-type: none"> • 1580 (Planned) • 1240 (Planned) 	Children (2-10 years)
V59P21	US	Safety and Immune Response of MenACWY with ProQuad® administered at various schedules	Open-Label, Randomized Phase 3 Multi-Centre	<ul style="list-style-type: none"> • MenACWY followed by MenACWY plus ProQuad® SC • MenACWY followed by MenACWY IM followed by ProQuad® • ProQuad® SC 	<ul style="list-style-type: none"> • 610 (planned) • 610 (planned) • 610 (planned) 	Infants (7-9 months)
V59P22	Germany	Safety and Immune Response of One or Two Doses of MenACWY vs. Menjugate®	Open-Label, Randomized, Active Controlled Phase 3 Multi-Centre	<ul style="list-style-type: none"> • MenACWY • Menjugate® IM 	<ul style="list-style-type: none"> • 400 Planned • 200 Planned 	Infants (6 months)

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

A GCP inspection of 2 clinical sites, protocol numbers V59P13 and V59P18 and an inspection of the sponsor in connection with the examination of the current application was requested by the CHMP. The outcome of this inspection and the satisfactory responses to its findings are an integral part of this procedure. The overall recommendation was that clinical data could be used for further assessment. No additional GCP inspection actions prior to authorisation were required.

Pharmacokinetics

No pharmacokinetic studies were conducted. As explained in the European Medicines Agency Note for Guidance on “the Clinical Evaluation of New Vaccines”, pharmacokinetic studies are generally not required for vaccines. The kinetic properties of antigens do not provide useful information for determining dose recommendations.

Pharmacodynamics

The pharmacodynamic profile is defined by its immunogenicity profile. Since the efficacy of MenACWY vaccines is assessed by immunological criteria, all clinical studies will be discussed under Clinical Efficacy.

Clinical efficacy

- Immunological assays

The immune response elicited by meningococcal vaccines is demonstrated through an assay which measures the serum bactericidal activity from the serum of vaccine recipients. This in vitro assay tests the ability of vaccine-induced bactericidal antibodies to kill meningococci, when in the presence of complement. The hSBA was used exclusively in the development of MenACWY vaccine.

A validation report for the serum bactericidal assay for the determination of complement fixing antibodies against *Neisseria meningitidis* serogroups A, C, W135, and Y has been presented. Using a number of test sera the accuracy, precision, linearity and specificity was determined using a standard design for validation. The method was found to fulfil the set criteria for the different properties and therefore suitable for measuring clinical samples for documentation of immunogenicity.

The SBA test as such has been adequately validated. On request the company described the procedures regarding their cultivation of the target strains and selection of complement and sera. The choice of the target strains for serogroup A and C was based on the recommendations by Maslanka et al 1997 and the WHO and for serogroup W and Y available strains recommended by VEU or CDC were chosen.

The applicant has provided additional information which assures a high standardization of the hSBA assay.

ELISA is an alternative measure of immunogenicity according to the WHO guidelines. The Applicant has measured the immune response by ELISA measuring specific antibodies against the different capsule polysaccharides of the different serogroups in two ways: total IgG and high avidity antibodies. ELISA results have been presented from study V59P1, V59P2 and V59P3. In several of the clinical studies (V59P1, V59P2, V59P3, V59P6) immunogenicity has been measured by two or more of the following methods using the same set of sera:

- a. Serum bactericidal assay using human complement
- b. Serum bactericidal assay using baby rabbit complement
- c. ELISA measuring total serogroup specific IgG ($\mu\text{g/ml}$)
- d. ELISA measuring high avidity antibodies

On request a discussion regarding the significance of the different methods and correlation between these was submitted. The correlation of hSBA and rSBA (baby rabbit complement) was rather weak. The results with the testing of sera with rabbit complement demonstrated that subjects with hSBA <1:4 could still be considered protected according to the results of the rSBA.

- Dose response studies

Early dose response studies (**V59P1 & V59P3**) demonstrated the safety and immunogenicity of MenACWY, with or without aluminium phosphate as an adjuvant, in adults.

Study V59P1

Study V59P1 was designed to evaluate the safety and immunogenicity of a single dose of a MenACWY conjugate (CRM197) vaccine compared to separate, concomitant administration of the meningococcal A component (adjuvanted to aluminium phosphate) and MenCWY full liquid vaccine, and compared to a polysaccharide MenACWY vaccine (Mencevax®). This early clinical study demonstrated that a single dose of the tetravalent MenACWY vaccine conjugated to CRM197 (10µg of each antigen) was safe and well tolerated in healthy adults aged 18-45 years. Immune responses were comparable among vaccination groups, as expected for these vaccines (polysaccharide and primary conjugate) in adults.

In study V59P1, 15 subjects out of the 30 in each group were selected for the follow up study V59P1E1 which was set up to provide serological data from vaccinees challenged with a sub-optimal dose of Men A,C,W, Y polysaccharides 1 year after the primary vaccination. The subjects were randomly selected for the extension phase. There is some indication from this follow up study that MenACWY has a reduced capacity to induce a booster response compared to a monovalent conjugate vaccine. The Applicant commented on request that differences between populations as well as inherent variability with the hSBA assay are factors that contribute to differences in response.

Study V59P3

In study V59P3 (a phase I, observer blind, randomised controlled study) the safety and immunogenicity of a MenACWY conjugate vaccine with aluminium phosphate adjuvant was compared to a non-adjuvanted conjugated MenACWY vaccine and to a polysaccharide MenACWY vaccine (Mencevax®), in healthy adults. The conjugate MenACWY formulations were not associated with clinically significant safety concerns and were generally well-tolerated, with reactogenicity profiles similar to the MenACWY polysaccharide vaccine. Both conjugate vaccine formulations were immunogenic and induced IgG anticapsular antibody titres, as measured by total IgG Enzyme-Linked ImmunoSorbent Assay (ELISA).

According to the protocol of study V59P3, SBAs should have been analysed – however, because the primary objective was safety no bactericidal testing was performed and immune response was measured by ELISA, which is considered acceptable for this study.

The results from both Phase 1 studies (V59P1 & V59P3) supported further evaluation of the MenACWY conjugate vaccine formulations either with or without aluminium phosphate adjuvant in younger age groups. The selection of dose and the decision not to use an adjuvant in the final product were based on three randomized, observer- or double-blind, controlled clinical studies in children aged 12 to 35 months, an age group where it was predicted that a single vaccine dose might be most discriminating between candidate vaccines (V59P2, V59P4 and V59P7).

Study V59P2

Study V59P2 enrolled 600 toddlers aged 12 to 16 months into one of six vaccination groups. Four groups received one injection of adjuvanted MenACWY dose of each serogroup ranging from 2.5µg to 10µg. Based on pre-clinical data suggesting possible interference between the serogroup A antigen and the other serogroups, the study included a fifth group, which received 10µg of serogroups C, W and Y, omitting serogroup A. The sixth group, acting as the control arm, received Menjugate (serogroup C only). A subset received a second vaccination of the same vaccine and formulation that they had received at study day 1.

The results of this larger dose finding study, demonstrated that a 10µg-5µg-5µg-5µg dose combination for serogroups A, C, W-135 and Y, gave the best response expressed as GMT in toddlers, age 12-16 months.

Study V59P2 provided some evidence that the immune response against a monovalent conjugate MenC vaccine (Menjugate) was better as compared to the response to the (adjuvanted) MenACWY 10-5-5-5 vaccine for the MenC antigen. The result was supported by measuring capsular IgG antibodies by ELISA. This is possibly due to the higher content of MenC in the monovalent vaccine (10µg compared to 5µg in Menveo), however too little data has been presented to make any conclusions on the relevance of the observed difference. In their response the applicant presented on request briefly data from two studies in infants that were not submitted with the application. One of the studies indicated a better response of Menjugate compared to MenACWY against the MenC component while the other study indicated a similar response. Because the MenC component is important in the EU it is important to clarify the performance of a tetravalent versus monovalent vaccine. The Applicant has committed to submit the study protocol for V59P22 with a time table that shows when the information can become available.

In study V59P2 the hSBA GMT was significantly higher for most of the groups at the German investigation site compared to the Finnish site. The Applicant discussed potential causes of the large variation between the two sites. Also, in this study the ELISA method for measuring capsular IgG antibodies was discontinued because ELISA results were considered unreliable as a correlate for protection.

Studies V59P4 and V59P7

Study **V59P4** enrolled 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.

Study **V59P7** enrolled 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.

Both studies **V59P4 and V59P7** demonstrated that the short term immunogenicity was only marginally increased with the addition of aluminium phosphate, justifying the choice for the non-adjuvanted 10-5-5-5 MenACWY formulation. Study V59P6 confirmed the marginal effect of the adjuvant (see section on supportive studies).

Following the initial assessment there was not enough data to conclude if the addition of aluminium adjuvant affects the long term persistence of bactericidal antibodies. In an extension of study V59P4 (amendment 5), for a selection of subjects antibody persistence was evaluated at 12 months. Data for MenC antibodies at 12 months provided no indication that the presence of aluminum phosphate adjuvant in the MenACWY formulation affected the immune response to MenC. There was no significant difference at day 360 between the 5ACWY(-alum) and 5ACWY(+alum) formulations in either hSBA GMTs or % responders ($\geq 1:4/\geq 1:8$). The response to the 10ACWY(-alum) formulation did not differ significantly from the 5ACWY(-alum) or 5ACWY (+alum) formulations. According to the original Study Report of V59P4, the persistence of antibodies to N meningitidis serogroups A, C, W135 and Y at 12 months following immunization would be evaluated. It is appreciated that the presence of the adjuvant did not significantly increase the % with hSBA $\geq 1:4$ and $1:8$ to serogroup C at day 360 compared with the non-adjuvanted MenACWY formulation. No further testing at day 360 was performed for the other serogroups.

Study V59P7 showed a low response to the MenC component. The GMT values presented showed some inconsistencies, as the 6-month titre was higher than the titre measured 1 month post vaccination. Also, the proportion of subjects with titre $\geq 1:8$ (36%) and with titre $\geq 1:4$ (49%) were both lower than those observed in study V59P4. The applicant discussed that the difference in

response in different studies might be due to several contributing factors for example different vaccine formulations and different populations.

- Main studies

The clinical program included one pivotal study (V59P13) and four supportive studies (V59P6, V59P17, V59P18 and V59P11).

There were three primary immunogenicity objectives for these studies:

- 1) Assess non-inferiority versus a licensed comparator (Menomune licensed in EU or Menactra licensed in the US);
- 2) Establish clinical lot consistency for MenACWY;
- 3) Establish non-interference with age-appropriate vaccines on the immunogenicity of MenACWY due to
 - a) concomitant vaccination with Tdap (Boostrix) and HPV (GARDASIL) vaccine
 - b) sequential vaccination 1 month following Tdap vaccine.

Methods (general)

The basic methodology of the clinical development plan for the MenACWY vaccine (as inclusion and exclusion criteria, the definitions for the immunologic, safety, and statistical endpoints) was conserved across all phase III studies. Specific objectives and populations under study varied. The same laboratory techniques used for the hSBA assays were used in each study. Unless specified otherwise, the immunogenicity of each vaccine was tested one month post vaccination.

Study V59P13

The pivotal study, V59P13, was a randomised single blind controlled multicentre study to evaluate lot-to-lot consistency of MenACWY and to compare safety and immunogenicity of MenACWY with that of Menactra™ (Meningococcal ACWY Conjugate Vaccine).

METHODS

Study participants

Study participants were healthy male and female individuals, aged 11 to 55 years, recruited from local communities (44 centres) within the US. Next to general exclusion criteria common for most vaccine trials, specific exclusion criteria were:

- A previous or suspected disease caused by *N meningitidis*,
- A household contact with and/or intimate exposure to an individual with culture-proven *N meningitidis* infection within 60 days prior to enrolment,
- Previously immunized with a meningococcal vaccine or vaccine containing meningococcal antigen(s) (exception: receipt of Outer Membrane Protein (OMP)-containing *Haemophilus influenzae type b* (Hib) vaccines was permitted).

Treatments

Individuals were assigned to receive either the investigational vaccine MenACWY Lot 1, MenACWY Lot 2, MenACWY Lot 3, or Menactra.

One 0.5 ml dose of the final MenACWY formulation (10-5-5-5) or 0.5 ml dose of Menactra (4µg of polysaccharide conjugated to diphtheria toxoid) was administered by intramuscular (IM) injection in the left deltoid area.

The comparator, Menactra, is not licensed in EU; it was licensed in the USA and Canada based upon demonstrating immunological equivalence of Menactra with a polysaccharide tetravalent meningococcal vaccine (Menomune).

Objectives

The primary objectives of V59P13 were:

- To establish clinical lot-to-lot consistency between three lots of MenACWY with respect to hSBA GMTs, in adolescents aged 11 to 18 years. Lot-to-lot consistency was established if for all serogroups and for all pairs of vaccine lots, the two-sided 95% CI of the GMT ratio was within [0.5, 2.0].
- To demonstrate non-inferiority of MenACWY compared with Menactra, as measured by the percentage of subjects with seroresponse in adolescents aged 11 to 18 years, and in adults aged 19-55 years. For all of the four serogroups, the lower limit of the two-sided 95% CI around the difference (MenACWY minus Menactra) in the percentage of subjects with seroresponse had to be greater than -10% to accept non-inferiority.

Secondary objectives were:

- To establish clinical lot-to-lot consistency between three lots of MenACWY, as measured by the percentage of subjects with seroresponse and hSBA titre $\geq 1:8$, in adolescents aged 11 to 18 years.
- To demonstrate non-inferiority of MenACWY compared with Menactra, as measured by the percentage of subjects with seroresponse (ages 11 to 55 years), hSBA titre $\geq 1:8$ and $\geq 1:4$ and GMTs (ages 11 to 18, 19 to 55, and 11 to 55 years).

Blood was drawn before vaccination at day 1, and after vaccination, at day 29. From day 29 to day 180 only safety was collected.

Outcomes/endpoints

Primary and secondary immunogenicity endpoints are described above.

Seroresponse was defined as a composite endpoint:

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

Samples Size

Primary Lot-to-Lot Consistency:

Within-group standard deviations were estimated based upon results in study V59P6. In order to ensure high power for serogroup C, 525 subjects were planned to be randomized to each of the three MenACWY lots to obtain 500 evaluable subjects. In order to maintain the 1:1:1:1 treatment group balance in the randomization, 525 Menactra subjects were also planned to be enrolled. In addition, in order to conserve human complement donor resources for A, W, and Y, it was decided to assay a smaller number of evaluable subjects (350) for each of these serogroups. With 500 evaluable subjects per lot assayed for serogroup C and 350 evaluable subjects per lot assayed for serogroups A, W, and Y, the power to reject the null hypothesis associated with the primary lot-to-lot immunogenicity objective and to demonstrate immunologic consistency for each serogroup is 97%, >99%, >99%, >99% for C, A, W, and Y, respectively. Assuming the results for the four serogroups are independent, the overall power to demonstrate immunologic consistency is equal to 96%.

Primary Immunogenicity/Seroresponse:

It was assumed that the percentage of subjects in the adolescent group (11-18 yrs) with seroresponse is similar in the MenACWY group compared with Menactra. With 1500 evaluable subjects assayed for MenACWY serogroup C (i.e. three lots with 500 subjects, see above), 1050 evaluable subjects assayed for MenACWY serogroups A, W, and Y, 350 evaluable subjects assayed for Menactra serogroup A, 500 evaluable subjects assayed for Menactra serogroup C, and 300 subjects assayed for Menactra serogroups W and Y, the power to reject the null hypothesis associated with the non-inferiority immunogenicity primary objective and demonstrate non-inferiority for each serogroup is 99% for each of the serogroups A, C, W, and Y. Assuming the results for the four serogroups are independent, the

overall power to demonstrate immunologic non-inferiority is equal to 96%. Applying the same assumptions used for the adolescent group (11-18 yrs) to the adult group (19-55 yrs), the overall power to demonstrate immunologic non-inferiority in the adult group is estimated to be 90%. The estimate of the overall power across the three primary objectives is 83% (=96% x 96% x 90%).

Randomisation

In total, 3539 subjects 11 to 55 years of age were randomised at a 1:1:1:1 ratio to one of four vaccine groups (MenACWY Lot 1, Lot 2, Lot 3, or Menactra). Randomisation was stratified by centre and age so that 2180 adolescents (11 to 18 years of age), 413 adults (19 to 34 years of age) and 946 adults (35 to 55 years of age) were enrolled.

Blinding (masking)

Subjects were given MenACWY or Menactra intramuscularly (IM) by an unblinded study vaccine administrator. The subjects were blinded to the study vaccine given. All safety follow-up performed by the investigator and study staff was also blinded.

Statistical methods

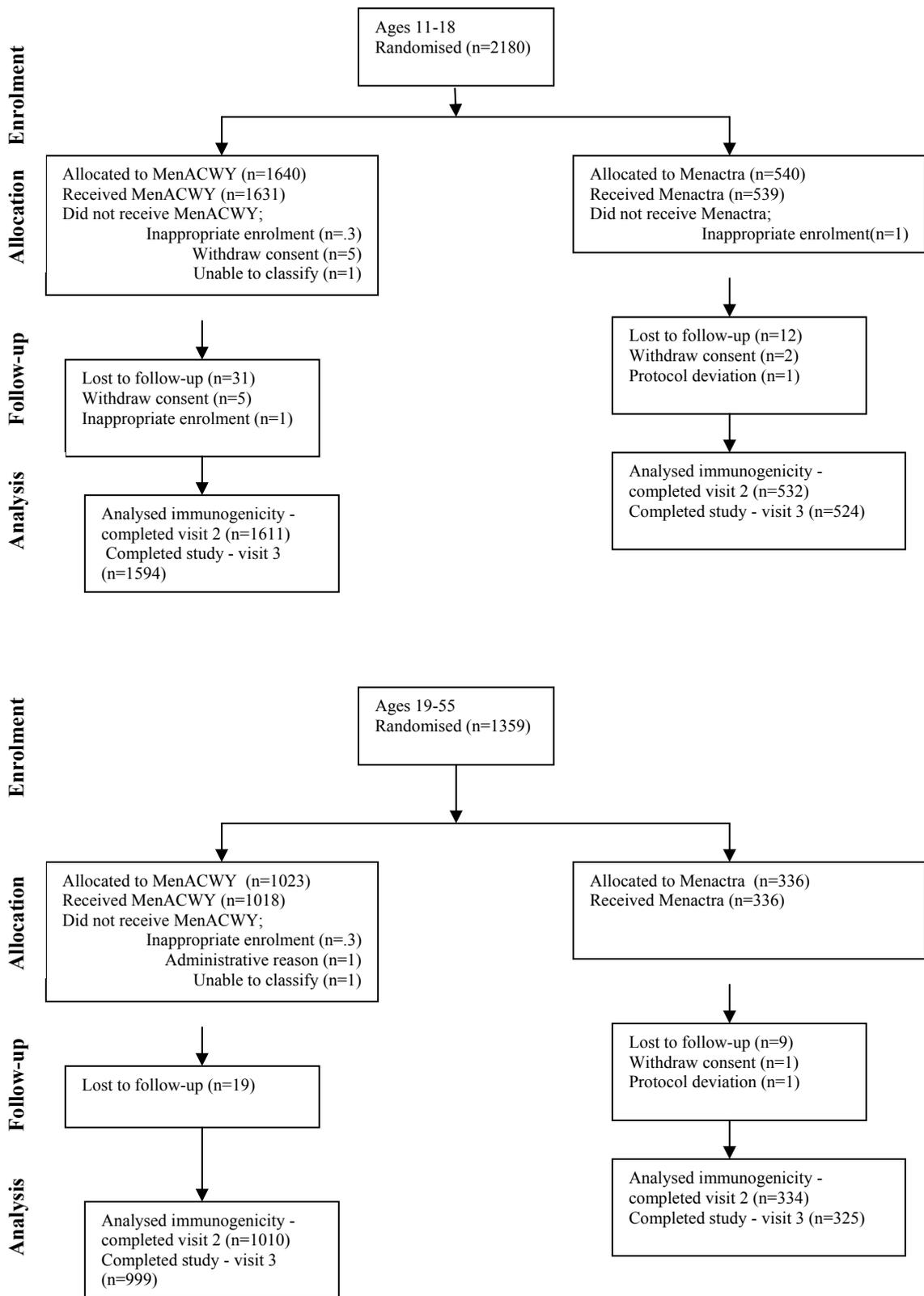
The GMTs, GMRs and two-sided 95% CIs were constructed by exponentiation (base 10) of the least square means of the logarithmically transformed (base 10) hSBA titers and their 95% CIs obtained from an Analysis of Variance (ANOVA) model with vaccination lot and center as factors in the model. As a sensitivity analysis to incorporate possible baseline imbalance among the lots, an analysis of covariance (ANCOVA) was also run which incorporated baseline log₁₀ titers and status for DT-containing vaccination in prior 5 years (status = with or without such vaccination) along with lot and center as factors in the model.

The two-sided 95% CIs for each serogroup for the difference in proportions (MenACWY minus Menactra) were constructed using the differences of two percentages based on the chi-square method. As a sensitivity analysis, a logistic regression was performed which incorporated baseline log₁₀ titers and status for DT-containing vaccination in prior 5 years along with group and center as factors in the model. Centers were combined as for the lot-to-lot consistency modelling.

For the local and systemic reaction safety variables, differences between the vaccine groups after vaccination with respect to all variables (including fever) were analysed using Pearson's chi-square test, or Fisher's Exact test where appropriate due to small expected cell sizes.

RESULTS

Participant Flow



Recruitment

The first subject was enrolled on 1st March 2007; the last visit was completed on 16th January 2008.

Conduct of the study

The original study protocol, issued on Oct. 9, 2006, was followed by two amendments.

The first amendment, issued on May 21, 2007, was to incorporate changes recommended through regulatory feedback, provide clarification regarding responsibilities of study personnel, and define the coordinating investigator and sites, included seven major and six minor changes. Two former immunogenicity secondary objectives were changed to become primary objectives, the immunogenicity endpoint “4-fold rise in hSBA titre” was changed to “seroresponse”, the number of adults in the 35 to 55 year old age stratum was increased by 400 subjects, and medical history, safety assessment, and exclusion criteria were revised.

A second amendment was issued on December 20, 2007 to: (a) revise the evaluation of non-inferiority of MenACWY to Menactra by increasing the size of the subset of subjects to be analyzed for each of the four serogroups and by modifying the calculations of the power to demonstrate non-inferiority and (b) clarify that the immune response for examining lot-to-lot consistency would also be measured by the percentage of subjects with seroresponse and hSBA titre $\geq 1:4$ and $\geq 1:8$. All analyses planned in the AP (defined and approved before data base lock) were performed. No post hoc analyses were performed.

Baseline data

Demographic and other baseline characteristics were similar for the subjects 11-18 years of age randomised to receive one of the three MenACWY lots. The baseline characteristics were also similar for the subjects 11-55 year of age randomised to receive either MenACWY or Menactra. A larger proportion of women vs men was recruited in the age group 19-55.

Numbers analysed

It was planned to enrol 3432 subjects. In total, 3539 subjects were enrolled and randomized to receive either MenACWY (lot 1, lot 2, lot 3) or Menactra. Of the 3524 subjects that received a vaccine, 2649 received MenACWY and 875 received Menactra. The overall PP populations consisted of 3393 subjects, 2549 in the MenACWY group and 844 in the Menactra group, corresponding to 96% of the enrolled population in both vaccine groups.

Outcomes and estimation

Primary and Secondary Objectives Lot to Lot consistency (in the 11-18 age group):

The objective of demonstrating lot to lot consistency for the primary endpoint, hSBA GMTs, was achieved for all serogroups. However, it was not achieved for the secondary outcomes for all serogroups.

Primary Immunogenicity Objectives:

The results for the other primary objective (i.e. demonstrating non-inferiority in seroresponse as compared to Menactra one month following vaccination) are presented in the following table.

Seroresponse: Non-inferiority (11 to 18 year, and 19 to 55 year age groups)

		11-18 years			19-55 years		
		MenACWY	Menactra	Vaccine Group Difference (95% CI)	MenACWY	Menactra	Vaccine Group Difference (95% CI)
A	Baseline titre <1:4	75%	66%	9%	67%	67%	-1%
		780/1039	230/347	(3%, 15%)	582/875	191/283	(-7%, 5%)
	$\geq 1:4$	58%	67%	-8%	70%	71%	-1%
		21/36	8/12	(-35%, 24%)	62/88	27/38	(-17%, 18%)
	Overall	75%	66%	8%	67%	68%	-1%
		801/1075	238/359	(3%, 14%)	644/963	218/321	(-7%, 5%)
C	Baseline titre <1:4	79%	79%	0%	71%	62%	9%
		771/977	260/331	(-5%, 6%)	425/596	133/214	(2%, 17%)

		$\geq 1:4$	68%	62%	6%	61%	51%	10%
	Overall		345/506	105/170	(-2%, 15%)	223/365	53/104	(-1%, 21%)
			75%	73%	2%	67%	58%	9%
			1116/1483	365/501	(-2%, 7%)	648/961	186/318	(3%, 15%)
W	Baseline titre	<1:4	94%	83%	10%	82%	71%	11%
			570/609	150/180	(5%, 17%)	131/160	67/94	(0%, 22%)
		$\geq 1:4$	47%	28%	19%	35%	26%	8%
	Overall		193/415	30/108	(9%, 28%)	112/324	52/198	(0%, 16%)
			75%	63%	12%	50%	41%	9%
			763/1024	180/288	(6%, 18%)	243/484	119/292	(2%, 17%)
Y	Baseline titre	<1:4	81%	54%	27%	66%	52%	14%
			510/630	95/176	(19%, 35%)	173/263	83/160	(4%, 23%)
		$\geq 1:4$	47%	22%	25%	45%	27%	18%
	Overall		192/406	26/118	(16%, 34%)	108/240	39/146	(9%, 28%)
			68%	41%	27%	56%	40%	16%
			702/1036	121/294	(20%, 33%)	281/503	122/306	(9%, 23%)

The immune response to MenACWY was found to be non-inferior to the immune response against Menactra in both adolescents and adults according to the predefined margins. However, as can be seen in the table above, seroresponse was relatively low. This appeared to be mostly driven by the low response in subjects who had baseline hSBA $\geq 1:4$, and the relatively high proportion of subjects with baseline hSBA $\geq 1:4$ in serogroups C, W and Y.

After first review of the data the lower seroresponse in subjects with prevaccination hSBA $\geq 1:4$ as compared to subjects with baseline hSBA < 1:4 in the pivotal study raised the concern of potential hyporesponsiveness. The applicant provided data and discussed the relevance of pre- and postvaccination GMTs in addition to seroresponse. These are summarised in the table below for subject seropositive and seronegative at baseline separately:

	Baseline titre			
	<1:4		$\geq 1:4$	
Serogroup	Pre Vaccination GMT (95% CI)	Post Vaccination GMT (95% CI)	Pre Vaccination GMT (95% CI)	Post Vaccination GMT (95% CI)
A	2.01 (1.98 – 2.05)	28 (23 – 34)	13 (12 – 14)	91 (50 – 166)
C	2 (1.9 – 2.11)	37 (30 – 46)	11 (11 – 12)	152 (118 – 195)
W	1.9 (1.77 – 2.04)	59 (50 – 70)	36 (33 – 39)	153 (128 – 183)
Y	1.92 (1.79 – 2.05)	35 (29 – 43)	18 (17 – 20)	82 (66 – 102)

The post vaccination GMTs for subjects with baseline hSBA titre $\geq 1:4$ are higher as compared to subjects who were seronegative at baseline, with a higher absolute increase. This supports that there is no evidence of a reduced antibody response in seropositive persons and /or an indication of hyporesponsiveness.

Secondary Immunogenicity Objectives:

The percentages of subjects aged 11-55 years old with baseline hSBA titre $\geq 1:8$ at day 1 were similar between the two vaccine groups. At day 29, the percentages of subjects with hSBA titre $\geq 1:8$ showed

a large increase for all four serogroups in both vaccine groups but were consistently higher in the MenACWY group (A: 72% vs. 69%, C: 83% vs. 79%, W: 95% vs. 89%, Y: 85% vs. 70%).

The results for the secondary objectives confirm the findings for the primary objectives; for the entire study population (PP) non-inferiority can be demonstrated. The proportion of subjects with hSBA titres $\geq 1:8$ one month after vaccination is reassuringly high, although a relatively high proportion of seropositive subjects at baseline was observed, especially for serogroup W135.

Ancillary analyses

A larger proportion of **women versus men** was recruited in the age group 19-55. Upon request the MAH showed that both the immunogenicity results from study V59P18 (% subjects with hSBA $\geq 1:8$) as from study V59P13 (hSBA GMTs) stratified by gender did not provide any evidence of an effect of gender on the immune response to MenACWY.

- Clinical studies in special populations

The MAH presented supplementary immunogenicity data (hSBA GMTs, % subjects with hSBA $\geq 1:4/1:8$) from 83/84 subjects between the ages of 56 and 65 years (addendum of CSR V59P17). The responses in the MenACWY group were consistently higher as compared to the Menomune group. More importantly, the response in the older age group (56-65 years) was not lower as compared to the response in the 18-55 years age group. The results from study V59P13 stratified by 10 year age strata did not provide evidence of a consistent declining immune response with increasing age. Nevertheless, there is some indication of a decline with increasing age, most notably for serogroup Y.

- Supportive studies

Study V59P6

V59P6 was a phase 2, randomized, single-blind, controlled, multi-centre study which provided further data on the immunogenicity of MenACWY in 424 adolescents, this time compared to a polysaccharide MenACWY vaccine, Menomune. The initial objective of this study was to compare the immunogenicity and safety of MenACWY adjuvanted to aluminium phosphate to that of Menomune. However, after enrolment had started, the decision was made to continue with an unadjuvanted MenACWY vaccine, resulting in the addition of an extra stage and treatment arm in study V59P6.

The primary objective of study V59P6 was to compare the immunogenicity of a single dose of either the adjuvanted (MenACWY+) or unadjuvanted (MenACWY-) formulation of MenACWY conjugate vaccine with the immunogenicity of a single dose of licensed meningococcal ACWY polysaccharide vaccine (Menomune®), defined as % of subjects with hSBA $\geq 1:4$ directed against *N. meningitidis* serogroups A, C, W-135, and Y at 1 month after vaccination, when administered to adolescents 11 to 17 years of age. The study also looked at persistence of antibodies at 12 months post vaccination.

The primary endpoint (% of subjects with hSBA $\geq 1:4$) was unlike that of other trials within the development program of MenACWY, as it was not discriminative for subjects with pre-existing antibody titres against the different antigens. Nevertheless, the results of this trial provide useful supportive data, especially regarding the comparison with a PS MenACWY vaccine.

At one month after study vaccination, both MenACWY+ as MenACWY- vaccine groups showed significantly higher percentages of subjects with hSBA titres $\geq 1:4$ for all four serogroups as compared to Menomune. Although the threshold hSBA $\geq 1:4$ is considered to be a confident measure for short term clinical protection against invasive disease, the more conservative threshold of hSBA $\geq 1:8$ was preferred, based upon the intrinsic character of the hSBA as this uses the starting dilution of $\geq 1:4$. The results for V59P6 with % subjects hSBA $\geq 1:8$ are presented in the following table:

Percentage of subjects with hSBA \geq 1:8, Prevacination & 1 month post vaccination:

		% with hSBA \geq 1:8			
<i>Time of blood sample:</i>	Parameter	MenACWY +	MenACWY-	Menomune	
A	Prevaccination	n (%)	2 (1)	2 (1)	1 (1)
		95% CI	0-4	0-5	0.014-3
		N	158	148	179
1 month after vaccination		n (%)	128 (81)	120 (81)	74 (41)
		95% CI	74-87	74-87	34-49
		N	156	148	179
Censored	1 month after vaccination	n (%)	126 (81)	118 (81)	73 (41)
		95% CI	74-87	73-87	34-49
		N	156	146	174
C	Prevaccination	n (%)	20 (12)	25 (17)	32 (18)
		95% CI	8-19	11-24	13-25
		N	161	148	177
1 month after vaccination		n (%)	138 (86)	123 (83)	112 (63)
		95% CI	79-91	76-89	56-70
		N	161	148	177
Censored	1 month after vaccination	n (%)	118 (84)	98 (80)	80 (55)
		95% CI	79-91	71-86	47-63
		N	141	123	145
W	Prevaccination	n (%)	66 (41)	19 (13)	37 (21)
		95% CI	33-49	8-20	16-28
		N	161	146	173
1 month after vaccination		n (%)	156 (97)	132 (90)	149 (86)
		95% CI	93-99	84-95	80-91
		N	161	146	173
Censored	1 month after vaccination	n (%)	90 (95)	113 (89)	112 (82)
		95% CI	88-98	82-94	75-88
		N	95	127	136
Y	Prevaccination	n (%)	28 (18)	34 (23)	40 (23)
		95% CI	12-24	17-31	17-29
		N	159	147	177
1 month after vaccination		n (%)	149 (94)	139 (95)	143 (81)
		95% CI	89-97	90-98	74-86
		N	159	147	177
Censored	1 month after vaccination	n (%)	121 (92)	105 (93)	104 (76)
		95% CI	86-96	87-97	68-83
		N	131	113	137

censored: subjects seropositive at baseline removed from analysis

When comparing the immunogenicity elicited by MenACWY- (non-adjuvanted, final formulation) with Menomune (licensed polysaccharide vaccine), in the present study, the % subjects with hSBA \geq 1:8 one month post vaccination is higher for all serogroups for MenACWY.

After removal of seropositive subjects at baseline (defined as hSBA \geq 1:4) from the analysis (marked as “censored” in the table above), the percentage of subjects with hSBA \geq 1:8 one month post vaccination for all serogroups remained consistently high (81%, 84%, 95% and 92% for Men A, C, W, and Y respectively). This was confirmed by the secondary objective, hSBA GMTs. The results of this study are clearly supportive to the demonstration of efficacy by MenACWY (non-adjuvanted). The results of this study furthermore supported the choice of a non-adjuvanted formulation as compared to the adjuvanted MenACWY vaccine (i.e. the difference in response at one month between MenACWY- and MenACWY+ is minimal).

For Menomune the proportion of subjects with hSBA $\geq 1:4$ of 46% against MenA one month after vaccination was surprisingly low. Plain polysaccharide vaccines such as Menomune are expected to mount a high level of bactericidal antibodies that are protective against disease in this age group (11-17 years). In the earlier mentioned study, V59P4, Menomune was also used as a control vaccine and the proportion of subjects with hSBA titer $\geq 1:4$ against MenA was low for both Menomune (36% n=69) and MenACWY (41% n=70). Upon request the applicant explained the characteristics of the SBA assay using human or rabbit complement and emphasised that comparisons between vaccines are more valid when performed within the same study.

Regarding the persistence of antibodies, a relatively large decline in the % of subjects with hSBA $\geq 1:4$ for serogroup A was seen over 12 months (48% drop) compared to other serogroups (3%, 0% and 9% drop for C, W & Y respectively) and compared to the decrease observed for Menomune for serogroup A (2% drop). The MAH presented additional data regarding persistence of serum bactericidal antibodies from study V59P13E1, an extension of study V59P13 in which hSBA was measured at 21 months, with planned further evaluations, 3, 5 and 7 years after vaccination in a subset of participants. These data are presented in the following table (subjects were aged 11-19 years at vaccination).

<i>Serogroup</i>	<i>Menveo 1 month</i>	<i>Menactra 1 month</i>	<i>Menveo 21 months</i>	<i>Menactra 21 months</i>
<i>A</i>	75% (n=239)	66% (n=134)	36% (n=275)	25% (n=188)
<i>C</i>	85% (n=278)	83% (n=192)	62% (n=275)	58% (n=188)
<i>W-135</i>	96% (n=238)	94% (n=108)	84% (n=273)	74% (n=185)
<i>Y</i>	86% (n=239)	70% (n=108)	67% (n=275)	54% (n=188)

The data from V59P13E1 are reassuring in the sense that the initial drop in hSBA titres against serogroup A observed in study V59P6 does not continue at the same rate, but may have stabilized at a lower level. The results from sampling at 3, 5 and 7 years in study V59P13E1 will be important to verify and the applicant has commitment to provide follow-up data on this.

Long term persistence is especially important when the vaccine is not primarily intended for travellers' vaccination, but rather for community intervention. In this respect it is important that the Applicant has also presented supporting data from clinical trials in infants and children 2-10 years. The data supports the following: 1) hSBA titre against serogroup A drops substantially between 1 and 12 months post vaccination, 2) MenACWY performs better than the polysaccharide comparator vaccine (Menomune), and 3) a solid booster effect was observed after a small dose of polysaccharide or a new dose of vaccine.

In study V59P6 serum bactericidal titres were also measured by using baby rabbit complement in addition to the human complement. While human complement was used for the whole population of 148 subjects in the non-adjuvanted MenACWY group, the baby rabbit complement was used on a subset of 68 subjects. The samples for rSBA were randomly selected before the hSBA results were known. The results are presented in the tables below:

Percentages of Subjects with Rabbit SBA Titers $\geq 1:8$ (95% CI) at Baseline, 1 Month and 12 Months After Vaccination (Study V59P6)

Sero group	Time point	rSBA Titers $\geq 1:8$ (%, 95% CI)	
		ACWY	Menomune
A		N=68	N=70
	Baseline	37% (25, 49)	31% (21, 44)
	1 month post	100% (95, 100)	100% (95, 100)
	12 months post	100% (94, 100)	97% (89, 100)
C		N=69	N=70
	Baseline	16% (8, 27)	13% (6, 23)

Sero group	Time point	rSBA Titers $\geq 1:8$ (%, 95% CI)	
		ACWY	Menomune
	1 month post	100% (95, 100)	99% (92, 100)
		N=63	N=63
	12 months post	84% (73, 92)	67% (54, 78)
W		N=69	N=70
	Baseline	13% (6, 23)	11% (5, 21)
	1 month post	100% (95, 100)	100% (95, 100)
		N=63	N=63
	12 months post	97% (89, 100)	71% (59, 82)
Y		N=69	N=70
	Baseline	9% (3, 18)	10% (4, 20)
	1 month post	100% (95, 100)	99% (92, 100)
		N=63	N=63
	12 months post	97% (89, 100)	75% (62, 85)

Rabbit SBA GMTs (95% CI) at Baseline, 1 Month and 12 Months After Vaccination (Study V59P6)

Sero group	Time point	rSBA GMTs	
		ACWY	Menomune
A		N=68	N=70
	Baseline	8.88 (5.07, 16)	7.91 (4.69, 13)
	1 month post	8159 (6045, 11013)	3549 (2683, 4695)
		N=63	N=63
	12 months post	2462 (1683, 3603)	1127 (789, 1612)
C		N=69	N=70
	Baseline	3.41 (2.41, 483)	3.17 (2.28, 4.41)
	1 month post	1791 (1184, 2708)	917 (619, 1356)
		N=63	N=63
	12 months post	161 (78, 331)	67 (34, 132)
W		N=69	N=70
	Baseline	4.69 (3.05, 7.22)	3.5 (2.33, 5.26)
	1 month post	9259 (6934, 12364)	4598 (3495, 6048)
		N=63	N=63
	12 months post	1627 (870, 3044)	157 (87, 282)
Y		N=69	N=70
	Baseline	3.17 (2.3, 4.36)	2.8 (2.07, 3.8)
	1 month post	7573 (5045, 11366)	1441 (981, 2119)
		N=63	N=63
	12 months post	1389 (784, 2458)	105 (61, 179)

The response as measured by rSBA is much higher than when measured with hSBA. The results demonstrate that subjects with hSBA <1:4 can still be considered protected according to the results of the rSBA, which seems to be the more sensitive method. The GMTs presented demonstrate a good immune response as measured by rSBA, with significantly higher GMTs 1 month after vaccination as compared to the comparator vaccine, and a similar picture at 12 months (though the difference did not reach statistical significance for serogroup C).

Study V59P17

Study V59P17 was an observer-blind, randomised controlled phase III multicenter study to compare the safety and immunogenicity of one dose of MenACWY with that of a licensed conjugated MenACWY vaccine in subjects aged 19-55 years. In addition the immunogenicity and safety of one dose of MenACWY was compared to one dose of a licensed polysaccharide MenACWY vaccine in health subjects aged 56-65 years of age. At the time of the initial application, serology analyses were still ongoing, and only safety results were submitted. The immunogenicity results for the older adults were received upon request. These are presented in the following table.

Immunogenicity of MenACWY and ACWY-PS at baseline and one month after vaccination in adults aged 56-65 years.

		Percentage of Subjects With hSBA Titer $\geq 1:8$			hSBA GMTs		
		Menveo	ACWY-PS	Menveo minus ACWY-PS) (95% CI)	Menveo	ACWY-PS	Menveo / ACWY-PS (95% CI)
A	Day 1	11% (5, 20) N=83	7% (2, 20) N=41	4% (-10, 14)	2.71 (2.29,3.22) N=83	2.36 (1.85,3.01) N=41	1.15 (0.86,1.55)
	Day 29	87% (78, 93) N=83	63% (47, 78) N=41	23% (8, 40)	111 (70,175) N=83	21 (11,39) N=41	5.4 (2.47, 12)
C	Day 1	21% (13, 32) N=84	17% (7, 32) N=41	4% (-12, 18)	3.79 (3.03,4.73) N=84	3.56 (2.59,4.89) N=41	1.06 (0.72, 1.56)
	Day 29	90% (82, 96) N=84	83% (68, 93) N=41	8% (-4, 23)	196 (125,306) N=84	86 (45,163) N=41	2.27 (1.05, 4.95)
W	Day 1	67% (56, 77) N=82	67% (50, 81) N=39	0% (-17, 19)	17 (12,25) N=82	16 (9.55,28) N=39	1.04 (0.55, 1.99)
	Day 29	94% (86, 98) N=82	95% (83, 99) N=39	-1% (-9, 11)	164 (112,240) N=82	132 (76,229) N=39	1.24 (0.64, 2.42)
Y	Day 1	20% (12, 30) N=84	27% (14, 43) N=41	-7% (-24, 8)	3.9 (2.99,5.08) N=84	4.2 (2.87,6.14) N=41	0.93 (0.59, 1.47)
	Day 29	88% (79, 94) N=84	68% (52, 82) N=41	20% (5, 36)	121 (76,193) N=84	28 (15,55) N=41	4.25 (1.89, 9.56)

The proportion of subjects with hSBA titers $\geq 1:8$ was non-inferior to ACWY-PS for all four serogroups and statistically superior for serogroups A and Y. Similarly, GMTs were non-inferior to ACWY-PS for all four serogroups and statistically higher for serogroups A, C and Y.

Study V59P18

This Phase 3, open-label, single-center, randomised, controlled study in healthy subjects 11 to 18 years of age, evaluated the possible interference of concomitant or sequential administration of MenACWY, Tdap and HPV vaccines. In total, 1620 subjects were randomized at a 1:1:1 ratio to receive:

- MenACWY concomitantly with Tdap and HPV at study month 0 followed by two injections of HPV at month 2 and 6 (MenACWY+Tdap+HPV group);
- MenACWY at study month 0 followed by one injection of Tdap at month 1, followed by three injections of HPV at months 2, 4, and 8 (MenACWY → Tdap group);
- Tdap at month 0 followed by one injection of MenACWY at month 1, followed by three injections of HPV at months 2, 4, and 8 (Tdap → MenACWY group).

In this study there were numerous primary and secondary objectives of which several were interrelated.

The three primary objectives are described in the table below:

	Objective	Endpoint	Arms and timepoints to be compared:	Non-inferiority margin ¹ :
Primary Objective				
1	To show that the immunogenicity of MenACWY is not interfered with by concomitant administration of HPV and Tdap vaccines.	% Seroresponse	Group I vs. Group II at month 1	-10%
2	To show that the immunogenicity of Tdap is not interfered with by concomitant administration of MenACWY vaccine	% with anti-diphtheria toxin ≥ 1.0 IU/ml & anti-tetanus toxin ≥ 1.0 IU/ml Ratios of anti-PT, anti-FHA, anti-PRN GMC-s	Group I vs. Group III at month 1 Group I / Group III at month 1	-10% > 0.67
3	To show that administration of Tdap 1 month prior to MenACWY does not interfere with MenACWY response.	% Seroresponse	Group III at month 2 vs. Group II at month 1	-10%

Concerning the primary endpoints, the relevance of the definition of seroresponse for Diphtheria and Tetanus has been questioned – as subjects with prevaccination antibody titres are not accounted for. A different endpoint would have been more appropriate to evaluate the second primary objective (concerning interference with immune response to Tdap). Similarly, the significance of the defined endpoint for the pertussis antigens is not known as a correlate for protection.

Randomisation was stratified by gender.

Immune response to Men ACWY

The results for the primary MenACWY objectives of study V59P18 are presented in the table below:

Primary immunogenicity objectives (MenACWY): % of subjects with hSBA Seroresponse

Variable	MenACWY + Tdap + HPV (I)	MenACWY → Tdap ^a (II)	Tdap → MenACWY (III)	Vaccine Group Differences (95% CI)	
				Concomitant (I - II)	Sequential (III - II)

A	Baseline titer	<1:4	N=460 80% (76, 84)	N=456 81% (77, 85)	N=415 87% (84, 90)	-1% (-6, 4)	6% (1, 11)
		≥ 1:4	N=37 84% (68, 94)	N=30 87% (69, 96)	N=43 81% (67, 92)	-3% (-20, 16)	-5% (-22, 14)
		Overall	N=497 80% (77, 84)	N=486 82% (78, 85)	N=458 87% (83, 90)	-1% (-6, 4)*	5% (1, 10)**
C	Baseline titer	<1:4	N=337 90% (86, 93)	N=355 88% (84, 91)	N=319 90% (86, 93)	1% (-3, 6)	2% (-3, 7)
		≥ 1:4	N=160 69% (62, 76)	N=132 74% (66, 81)	N=138 69% (60, 76)	-5% (-15, 6)	-5% (-16, 5)
		Overall	N=497 83% (80, 86)	N=487 84% (81, 88)	N=457 84% (80, 87)	-1% (-6, 3)*	-1% (-6, 4)*
W	Baseline titer	<1:4	N=257 96% (93, 98)	N=259 99% (97, 100)	N=224 90% (86, 94)	-3% (-6, -1)	-9% (-14, -6)
		≥ 1:4	N=233 55% (48, 61)	N=215 59% (52, 65)	N=234 41% (35, 48)	-4% (-13, 6)	-17% (-26, -8)
		Overall	N=490 77% (73, 80)	N=474 81% (77, 84)	N=458 65% (61, 70)	-4% (-9, 1)*	-16% (-21, -10)
Y	Baseline titer	<1:4	N=362 91% (88, 94)	N=362 91% (87, 94)	N=333 90% (87, 93)	1% (-4, 5)	0% (-5, 4)
		≥ 1:4	N=134 59% (50, 67)	N=125 58% (48, 66)	N=127 46% (38, 56)	1% (-11, 13)	-11% (-23, -1)
		Overall	N=496 83% (79, 86)	N=487 82% (79, 86)	N=460 78% (74, 82)	0% (-4, 5)*	-4% (-9, 1)*

^a MenACWY alone

* noninferiority criterion met (the lower limit of the two-sided 95% CI >-10 %)

** superiority criterion met (the lower limit of two-sided 95% CI >0%).

There was no evidence to suggest that concomitant administration of MenACWY with Tdap & HPV vaccines had an effect on the immune response to MenACWY.

From these data there was some evidence to suggest that vaccination with Tdap one month prior to vaccination with MenACWY interfered with the immune response to MenACWY, as non-inferiority could not be demonstrated for MenW. In their response to this concern, the MAH focused on the relevance of postvaccination GMT and seroprotection in addition to seroresponse. However, also post vaccination MenW hSBA GMTs were lower for the group who received MenACWY one month after receiving a DTaP booster dose (hSBA GMT: 104, 95%CI: 91-119, vs. 159, 95%CI: 140-181 for the MenACWY→Tdap group), as was the % subjects with MenW hSBA ≥1:8 (95%, 95%CI: 93-97 vs. 99%, 95%CI: 98-100). Given the fact that seroprotection rates were still well above 90% and GMTs were high it is not very likely that the observed differences will be of major consequences.

Immune Response to Tdap

The results for the primary Tdap objective for study V59P18 are presented in the following table:

Primary immunogenicity objective: effect of concomitant vaccination on immunogenicity for Diphtheria, Tetanus, and Pertussis Antigens

MenACWY + Tdap + HPV (95% CI) (I)	MenACWY → Tdap (95% CI) (II)	Tdap → MenACWY ^{a)} (95% CI) (III)	Vaccine Group Difference (95% CI) (I - III)	Vaccine Group Ratio (95% CI) (I/III)
Concomitant				
N=495	N=459	N=487		

Diphtheria	% ≥1.0	100%	100%	98%	2%	NA
	IU/mL	(99, 100)	(99, 100)	(96, 99)	(1, 4)**	
Tetanus	% ≥1.0	100%	100%	100%	0%	NA
	IU/mL	(99, 100)	(99, 100)	(99, 100)	(-1, 1)*	
Pertussis antigen						
PT	GMC	N=482	N=452	N=477	NA	0.8
		51 (47, 55)	79 (73, 87)	63 (58, 69)		(0.71, 0.9)*
FHA	GMC	N=492	N=458	N=485	NA	0.67
		341 (310, 375)	1107 (989, 1238)	511 (464, 563)		(0.58, 0.76)*
PRN	GMC	N=495	N=459	N=487	NA	0.69
		824 (732, 928)	1563 (1390, 1758)	1198 (1063, 1351)		(0.58, 0.81)*

^a Tdap alone

* noninferiority criterion met (for D, T: the lower limit of the two-sided 95% CI >-10 %; **for PT, FHA, PRN: the lower limit of the two-sided 95% CI >0.67**)

** superiority criterion met (for D, T: the lower limit of two-sided 95% CI >0%; for PT, FHA, PRN: the lower limit of two-sided 95% CI >1.0).

Non-inferiority of the immune response to Tdap when administered concomitantly with MenACWY and HPV, compared with the immune response to Tdap when administered alone, was demonstrated for the diphtheria and tetanus antigens. One month after vaccination, nearly all subjects in both groups had antibody concentrations against diphtheria and tetanus ≥ 1.0 IU/ml. Although non-inferiority of Tdap with MenACWY & HPV to Tdap alone was established, prevaccination titres were high with up to 99% having achieved the endpoint for diphtheria and 87% for tetanus at baseline.

Regarding the antidiphtheria ELISA GMCs, a drop was observed in the GMC for Diphtheria from 26 (95%CI: 23, 28) at baseline to 10 (95%CI: 9.1, 12) 30 days after vaccination with Tdap in the MenACWY→Tdap group. The observed low anti-D response in this group is due to the GMTs being adjusted for baseline GMTs (log10 baseline) resulting in a less pronounced effect on anti-D. Experience from the use of other diphtheria toxoid containing vaccine has not indicated a safety concern. The higher response against diphtheria toxoid induced by Menveo as compared to Tdap is explained by the higher diphtheria toxoid content in MenACWY. MenACWY contains between 32.7 and 64.1 $\mu\text{g}/\text{dose}$ of CRM197 (based on the range of CRM as reported in the SPC), Tdap contains approximately 5 micrograms of diphtheria toxoid antigen per dose.

For the pertussis antigens, non-inferiority was demonstrated for PT but not for FHA or PRN. However, the clinical relevance of this finding is not clear since there are no established correlates of protection for pertussis. Also, it was found that subjects receiving Tdap one month after MenACWY had a better immune response to PT, FHA and PRN compared to those who received Tdap alone. Similarly, when comparing the % of subjects in the different groups with at least a four fold increase in antibody titre for PT, FHA and PRN, it appears that those who received Tdap one month after MenACWY had a better response compared to those who received the vaccines simultaneously. Here too, the clinical relevance is unknown.

Immune Response to HPV

With regards to the effect of concomitant administration of MenACWY with HPV vaccine on the immune response to the HPV vaccine, this was measured by anti-HPV seroconversion and anti-HPV GMTs one month following the third HPV vaccination. Non-inferiority of the immune response of HPV administered concomitantly with MenACWY and Tdap compared to HPV vaccine alone was demonstrated for the four HPV types for both endpoints, with seroconversion rates over 98% for all HPV types when HPV vaccine was administered concomitantly with MenACWY and Tdap and when administered alone. Nonetheless, anti-HPV GMTs were significantly lower when given with MenACWY and Tdap concomitantly.

	MenACWY + Tdap + HPV (95% CI) (I)	HPV alone (95% CI) (II + III)	Vaccine Group Ratio (95% CI) I/(II+ III)
HPV Type			
HPV 6	N=361	N=737	
GMT	1059 (926, 1212)	1461 (1327, 1608)	0.73 (0.62, 0.85)*
HPV 11	N=362	N=745	
GMT	1264 (1134, 1408)	1701 (1575, 1837)	0.74 (0.65, 0.92)*
HPV 16	N=492	N=458	
GMT	5286 (4705, 5939)	6590 (6068, 7158)	0.80 (0.70, 0.92)*
HPV 18	N=495	N=459	
GMT	908 (798, 1032)	1117 (1019, 1224)	0.81 (0.70, 0.95)*

* noninferiority criterion met (for D, T: the lower limit of the two-sided 95% CI >0.5)

Study V59P11

Study V59P11 was a phase 3 observer blind, randomised, controlled, multi-centre study, evaluating the immunogenicity and safety of concomitant administration of a Tdap Vaccine and MenACWY in healthy subjects aged 11 to 25 years.

The primary objective was to demonstrate non-inferiority of the immune response to a single injection of Tdap concomitantly administered with a single injection of MenACWY to a single injection of Tdap with placebo.

Immune response to Men ACWY

The immune response of MenACWY administered concomitantly with Tdap was evaluated in a subset of 245 randomly selected subjects. The results are presented in the following table:

MenACWY immunogenicity results of V59P11

		Geometric mean hSBA GMTs at day 1 and day 29 and GMRs		% subjects with hSBA titre ≥ 1:8 at day 1 and day 29	
Day	Variable	Tdap + MenACWY GMT/GMR (95%CI)	MenACWY + saline GMT/GMR (95%CI)	Tdap + MenACWY % of Subject (95% CI)	MenACWY + saline % of Subject (95% CI)
MenA		N=119	N=126	N=119	N=126
Day 1	<i>GMT</i>	2.14 (1.99, 2.31)	2.21 (2.05, 2.38)	2% (0%, 6%)	4% (1%, 9%)
Day 29	<i>GMT</i>	34 (23, 50)	50 (34, 74)	74% (65%, 82%)	80% (72%, 87%)
	<i>GMR (day 29/day 1)</i>	16 (11, 23)	23 (16, 33)		
MenC		N=118	N=124	N=118	N=124
Day 1	<i>GMT</i>	4 (3.23, 4.96)	3.92 (3.16, 4.86)	25% (17%, 33%)	25% (18%, 34%)
Day 29	<i>GMT</i>	89 (58, 136)	92 (60, 140)	92% (86%, 96%)	88% (81%, 93%)
	<i>GMR (day 29/day 1)</i>	22 (15, 33)	23 (16, 35)		
MenW		N=116	N=124	N=116	N=124
Day 1	<i>GMT</i>	11 (7.7, 15)	9.49 (6.93, 13)	53% (43%, 62%)	56% (46%, 65%)
Day 29	<i>GMT</i>	73 (54, 98)	77 (57, 103)	96% (90%, 99%)	97% (92%, 99%)

	<i>GMR (day 29/day 1)</i>	6.9 (4.84, 9.85)	8.09 (5.69, 12)		
MenY		N=117	N=125	N=117	N=125
Day 1	<i>GMT</i>	5.38 (4.2, 6.89)	5 (3.91, 6.39)	38% (30%, 48)	38% (29%, 47%)
Day 29	<i>GMT</i>	73 (54, 98)	70 (52, 94)	93% (87%, 97%)	94% (89%, 98%)
	<i>GMR (day 29/day 1)</i>	14 (9.41, 19)	14 (9.79, 20)		

There was no evidence of an effect of concomitant administration with Tdap on the immune response to MenACWY. The results for seroresponse clearly demonstrate an effect of baseline titre on response, which confirms the findings in earlier discussed studies.

Immune Response to Tdap

With regards to the effect of concomitant vaccination of MenACWY and Tdap on the immune response to Tdap, the results are presented in the following table:

Primary Immunogenicity Objective: % subjects in the Tdap-containing groups with anti-diphtheria and anti-tetanus titre ≥ 1.0 IU/ml and at least 4-fold increase for PT, FHA and PRN

Day	Variable	Tdap+ MenACWY % (95% CI)	Tdap + saline % (95% CI)	Vaccine difference (95% CI)
Diphtheria		N=350	N=345	
Day 1	≥ 1.0 IU/mL	4% (2%, 7%)	5% (3%, 7%)	0% (-4%, 3%)
Day 29	≥ 1.0 IU/mL	94% (91%, 96%)	85% (80%, 88%)	9% (5%, 14%)
Tetanus		N=350	N=345	
Day 1	≥ 1.0 IU/mL	25% (20%, 30%)	36% (31%, 42%)	-11% (-18%, 5%)
Day 29	≥ 1.0 IU/mL	100% (99%, 100%)	99% (98%, 100%)	1% (-1%, 2%)
PT		N=286	N=287	
Day 29	4-fold increase	76% (70%, 80%)	81% (76%, 85%)	-5% (-12%, 1%)
FHA		N=286	N=287	
Day 29	4-fold increase	83% (78%, 87%)	86% (82%, 90%)	-3% (-9%, 3%)
PRN		N=285	N=287	
Day 29	4-fold increase	84% (79%, 88%)	91% (87%, 94%)	-7% (-13%, -2%)

For diphtheria, the higher % of subjects achieving titres ≥ 1.0 IU/ml one month post vaccination in the Tdap+MenACWY arm (94%, 95%CI: 91-96%) as compared to the Tdap+saline arm (85%, 95%CI: 80-88%) can most likely be attributed to the presence of CRM197, the non-toxic mutant of diphtheria toxin, in MenACWY. The low level of responders at baseline (4-5%) is unlikely to have had an influence on this conclusion. With regards to tetanus, as both arms approach 100% of subjects with titres ≥ 1.0 IU/ml one month post vaccination, the difference between the two arms in baseline response does not affect the conclusions.

The results concerning the immune response against the pertussis antigens are in line with the results of study V59P18, although in this study it is the PT and PRN which are more affected by concomitant vaccination with MenACWY (compared to the FHA and PRN in study V59P18). Again, the clinical relevance of the difference between the two arms is unclear.

- Discussion on clinical efficacy

During the procedure, a concern was raised about the limited data in elderly adults and the unknown impact of age on immunogenicity. Since the number of exposed in the oldest age strata is low (n=84) and only includes persons up to 65 years of age, no final conclusions can be drawn regarding the influence on the immune response. Therefore, a statement has been included in the SPC that data in persons aged 55 to 65 are limited, and data in persons aged over 65 are absent.

In all studies a relatively high % of subjects had antibodies against MenW135 at baseline. This is unexpected as the incidence of disease due to serogroup W is low, and outbreaks are rare. The explanation given by the MAH is that baseline titres reflect presence of cross-reactive antibodies to subcapsular proteins in the selected serogroup W135 assay strain that contribute to complement-mediated killing as well as presence of specific W135 anti-capsular antibodies. The subsequent mathematical explanation that despite high baseline titres overcrowding may still lead to outbreaks, is a plausible hypothesis, but falls outside the scope of this assessment. Relevant is the interpretation of the hSBA results and extrapolation of these to protective efficacy that may be elicited by the vaccine. The Applicant was asked to clarify to what extent the subcapsular proteins contributed to the immune response of serogroup W, but also to other serogroups. It was clarified that the immune response to the vaccine is entirely driven by capsular polysaccharides, and therefore must be due to anti-capsular antibodies. The Company has committed to substantiate that the vaccine response to serogroup W is indeed specific, i.e. due to anti-capsular antibodies, and not due to (non specific) enhancement of immune response, which can be addressed by serum adsorption. This can be done in an ongoing or planned study.

Despite the methodology of study V59P13 being endorsed by CHMP during a scientific advice procedure, it has to be highlighted that in the scientific advice the company indicated that initial MA would be sought for children age 2 and older, and not 11 and older as is currently the case. Therefore, the relevance with regards to the European situation of the comparison with Menactra only as conjugated meningococcal vaccine would raise some concerns. The conditions and order of testing the several primary and secondary objectives were not clearly defined. Underlying assumptions as non-inferiority margins have not been carefully justified and placed into context of data from previous experience with PS MenACWY vaccines or conjugate MenC vaccines. The response of the MAH to the concern raised was not fully satisfactory. The choice of a non-inferiority margin should always be justified on a case by cases basis. Precedents from other regulatory authorities are not necessarily sufficient justification. In EMEA guidelines standard margins are proposed with the reservation that these margins may differ in different situations. However, although the MAH did not adequately address the issue, with few exceptions the results were such that it mainly concerned a methodological discussion without consequence for the current application. However, it should be very clear that these margins per se are not acceptable for future studies. The MAH has committed to adequately substantiate the margins for future studies.

During the procedure some concerns were raised regarding concomitant administration of Menveo with other vaccines. In study V59P18, it appears that administering MenACWY one month after administering of Tdap has a negative effect on the response to the W135 antigen (difference = -16%, 95%CI -21%, -10%). Given the fact that seroprotection rates were still well above 90% and GMTs were high it is not very likely that the observed differences will be of major consequences. However, this has been correctly reflected in the SPC. Also, there was some evidence to suggest a negative effect of concomitant vaccination with MenACWY and HPV on the response to pertussis antigens in studies V59P18 and V59P11. It is agreed with Applicant that the clinical relevance is unknown. The SPC has been updated accordingly.

Factors that have been identified to be critical for meningococcal vaccines to be effective for prevention of disease in a region, is to prevent carriage of the pathogenic strain and duration of serum bactericidal activity. As MenACWY may be used for that purpose in the future it is important that those factors are studied in more detail. Conjugated vaccines in contrast to plain polysaccharide vaccines have been shown to prevent carriage. The impact of vaccination on carriage is especially important when a vaccine is implemented in community vaccination programs. For the present intended use in travellers this is less relevant. However, this may change when the vaccine is planned

to be used in other (i.e. younger) age categories. The applicant has presented plans to study meningococcal carriage in response to vaccination. If possible the correlation between prevention of carriage and hSBA titers will also be studied by the applicant.

Clinical safety

The safety of the final non-adjuvanted 10-5-5-5 MenACWY formulation was evaluated in individuals aged 11 years and older in a series of phase 2 and 3 studies: V59P6, V59P11, V59P13, V59P17, and V59P18.

In addition, there is data available on severe adverse events (SAEs) reported from 11 studies with either different formulations or dosages, or in a different age group.

- Patient exposure

In the five main studies, a total of 6724 subjects were exposed to MenACWY as a single first vaccination or a second vaccination. In a pooled analysis, safety data for MenACWY was assessed from 6185 subjects aged 11 to 65 years, head-to-head comparisons were made with 1757 subjects who received Menactra, 209 subjects who received Menomune and 892 subjects receiving Tdap.

Patient exposure: studies with the final formulation and dose of MenACWY in the targeted age groups (>11 years)

Age Group Study	Number of Subjects Exposed Who Have Available Safety Data (Safety Population)					
	MenACWY Alone	MenACWY+ ConVax ^d	Total ACWY ^e	Menactra	Menomune	Tdap
11-18 years						
V59P6 ^a	151		151		209	
V59P11 ^b	357	359	716			353
V59P13	1631		1631	539		
V59P18 ^c	541	540	1081			539
19-34 years						
V59P13	307		307	105		
V59P17	838		838	464		
35-55 years						
V59P13	711		711	231		
V59P17	750		750	418		
Total	5286	899	6185	1757	209	892

a Subjects from V59P6 who received adjuvanted MenACWY are excluded.

b Subjects in V59P11 are 11 to 25 years of age.

c Subjects in V59P18 who received MenACWY followed by Tdap are included under the MenACWY column here and for the adverse events occurring during the first month after vaccination. Similarly, subjects who received Tdap followed by MenACWY are included under the Tdap column. Subjects from V59P18 are not included in the summaries of unsolicited adverse events occurring during the second through sixth months after vaccination. Data for the full duration of month 2 through month 6 are not yet available because this study is still ongoing.

d Subjects in V59P11 received MenACWY + Tdap (EU-marketed formulation); subjects in V59P18 received MenACWY + HPV + Tdap (US-licensed formulation).

e All subjects who received either MenACWY alone or with a concomitant vaccine (column 1 + column 2).

In addition, single or multiple injections of final or non-final MenACWY formulations were administered to subjects in the following age groups: V59P1 (adults aged 18 to 45 years), V59P2 (toddlers aged 12 to 16 months), V59P3 (adults aged 18 to 45 years), V59P4 (toddlers aged 12 to 16 months), V59P5 (infants aged 2 months), V59P7 (toddlers aged 12 to 35 months and children aged 36 to 59 months), V59P8 (children aged 2 to 10 years and toddlers aged 12 to 23 months), V59P9 (infants

aged 6 to 12 months), V59P10 (children aged 2 to 10 years), ongoing study V59P14 (infants aged 2 months), and ongoing study V59P16 (infants aged 2 months). For the two studies ongoing at the time of the submission, severe adverse events based on the safety database as of 15 February, 2008, were listed and evaluated.

- Adverse events

Solicited adverse events:

Solicited adverse events were categorized as local reactions, systemic reactions or other indicators of reactogenicity. An overview of all solicited adverse events for MenACWY and Menactra is presented in the following table (pooled analysis).

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

Local reactions

Injection site pain was noted as the most common local reaction during the 7 days after vaccination. Severe pain was reported in 2% for both vaccines. Injection site pain was mostly reported during the first 3 days after vaccination. Erythema was reported in 15% of subjects receiving MenACWY, severe erythema was reported in 2% of subjects receiving MenACWY. In the Menactra group this was

13% and 1% respectively. The onset of erythema was mostly in the first three days following vaccination.

The incidence of induration after MenACWY in pooled studies was 13%, induration greater than 50 mm was reported in 1% of subjects. For subjects receiving Menactra this was 12% and 1% respectively. The onset of induration was mostly within the first three days following vaccination. In study V59P13, there was one subject with an extensive site reaction (8x13 cm) following vaccination with MenACWY.

Systemic reactions

In total the incidence of chills, nausea, malaise, myalgia, arthralgia, headache, rash and fever was similar between the two vaccine groups. Headache was most commonly reported, followed by myalgia. The onset of systemic reactions was mostly reported within the first three days after vaccination, except for rash and fever, which were reported equally over the first seven days.

Other reactions

The incidence of subjects staying home during the 7 days after vaccination was 4% in both the total MenACWY group and in the Menactra group. Staying home was most frequently reported within the first 3 days after vaccination. The use of analgesic/antipyretic medication was 17% in the total MenACWY group and 19% in the Menactra group (pooled studies, pooled age groups). Medication use was mostly reported within 3 days after vaccination.

Unsolicited adverse events

During month 1 after vaccination, headache (outside the first 7 days) was the only AE that occurred with an incidence of 1% or more in the total MenACWY group. No difference in the incidence of headache was noted between the total MenACWY and Menactra groups (2% each). During months 2 to 6 (study V59P18 excluded), none of the AEs was reported by 1% or more of the subjects.

The overall incidence of unsolicited adverse events was low – mostly these concerned adverse events that fell outside the predetermined 7 day period in which they were solicited (i.e. headache, myalgia, nausea, induration, erythema, arthralgia, rash). The most frequently reported unsolicited AEs in the total MenACWY group were headache (2% incidence) and pharyngolaryngeal pain dysmenorrhoea, upper respiratory tract infection, cough, nausea, malaise, pharyngitis, and vomiting (all 1%). Concomitant administration of MenACWY and Tdap or Tdap+HPV did not affect the incidence of unsolicited AEs. None of the “probably or possibly related adverse events” reported during the first month after vaccination occurred in more than 1% of the subjects.

Summary of probably and possibly related unsolicited adverse events within 1 month after vaccination: MenACWY compared with Menactra in pooled age groups and pooled studies

	Total MenACWY N=6185	Menactra N=1757
Headache	62 (1)	20 (1)
Malaise	34 (1)	5 (<1)
Injection site erythema	32 (1)	2 (<1)
Injection site pain	28 (<1)	8 (<1)
Injection site pruritis	25 (<1)	5 (<1)
Myalgia	23 (<1)	7 (<1)
Nausea	23 (<1)	3 (<1)
Injection site induration	21 (<1)	1 (<1)
Arthralgia	18 (<1)	11 (1)
Erythema	14 (<1)	4 (<1)

Diarrhoea	13 (<1)	5 (<1)
Lymphadenopathy	13 (<1)	2 (<1)
Rash	13 (<1)	5 (<1)
Nasopharyngitis	12 (<1)	5 (<1)
Dizziness	10 (<1)	12 (1)
Pharyngolaryngeal pain	10 (<1)	5 (<1)
Induration	10 (<1)	2 (<1)

Criterion for inclusion in this table = 10 subjects in the total ACWY group. Cell entries are n (%).

There were no episodes of anaphylaxis or immediate hypersensitivity within 30 minutes after vaccination. One non-serious adverse event from V59P13 was of interest as an immune-mediated neurological syndrome, however, this event was considered unrelated to vaccination.

- Serious adverse event/deaths/other significant events

No deaths were reported during or after the study period in the five studies included for the proposed indication. Two subjects outside of the proposed indication died (one person of hypovolemic shock following the placement of a “double J stent”; one infant due to a lung infection). Both events were assessed as unrelated to study vaccinations.

Of the 6185 subjects receiving MenACWY included in the pooled safety analysis, 40 (0.6%) reported at least one SAE from vaccination day through the 6-month follow-up in the five studies supporting the proposed indication. SAEs reported by more than one subject each who received MenACWY were spontaneous abortion (4 subjects), appendicitis and road traffic accident (3 subjects each), and suicide attempt (2 subjects). One SAE was considered probably or possibly related to study vaccine: spontaneous abortion in a 19 to 34 year old subject in the V59P17 study. All other SAE were considered unrelated.

Serious Adverse Events in Completed Studies not included in the pooled safety analysis

Overall, there have been 292 SAEs reported up to 15 February 2008 in subjects who received any formulation of MenACWY, or in subjects for whom the vaccine remains unknown due to the blind nature of the studies that are ongoing. Among all SAEs reported in completed studies, five serious adverse events observed in infant trials were considered possibly related: febrile seizures (study V59P10), supraventricular tachycardia (study V59P5), idiopathic thrombocytopenic purpura (study V59P5), Kawasaki’s disease (V59P14), and infant botulism (V59P14).

- Laboratory findings

Clinical laboratory tests (chemistry, haematology, and routine urinalyses) were carried out on samples provided by participants in the first two studies, V59P1 and V59P3, conducted under the clinical development plan for MenACWY. No significant abnormal changes in laboratory parameters were seen.

- Safety in special populations

The possible effect of intrinsic factors (age and gender) and extrinsic factors (geographic location) on the safety results was evaluated.

Concerning age, it was found that the group 35-55 years old reported less adverse reactions compared to the younger age groups, indicating a decrease in reactogenicity with an increase in age. This is a known phenomenon for vaccines. Concerning gender, it was found that female subjects reported more

adverse events compared to male subjects, primarily regarding injection site pain (F:46%, M:34%), and headache (F: 35%, M:24%) and “stayed home” (F:20%, M:13%). As the difference in the safety profile for males and females is similar for both vaccine groups it does not affect the comparison of safety between MenACWY and Menactra. Overall, there is paucity of data in subjects over 55 years. In study V59P17 safety data was collected for subjects between 56 and 65 years of age, these data were not integrated in the integrated summary of safety because these data are the only safety data generated in that age group therefore integration was considered not necessary.

Regarding geographic location, the safety data from subjects out of the US was compared to that of the Latin American population. The only real difference between the two populations is in the reporting of malaise, which is higher in the Latin American population, and to some degree the higher incidence of chills in the Latin American population. This finding is considered to be of marginal importance.

Use in Pregnancy and Lactation

Thirty four women in studies V59P13 and V59P17 became pregnant during the 6-month follow-up period. Twenty-eight women were administered MenACWY, and six women were administered Menactra. For 22 subjects, the pregnancy is ongoing, and is being monitored. In these studies there have been four miscarriages, five therapeutic abortions, and one congenital anomaly. One spontaneous abortion in V59P17 was judged related to the study vaccine due to temporal relation. The listings and overview of miscarriages or spontaneous abortions however did not seem to be complete and accurate. However the Company has adequately explained the differences in the numbers tabulated. From the clinical reports of single studies 5 spontaneous abortions/ miscarriages were identified.

One further case of miscarriage/spontaneous abortions was observed in study V59P18, however, follow-up on the pregnancy status was not performed in this study.

Elderly

Data in subjects aged 56-65 year is still limited and no data is available in subjects aged > 65 years.

- Safety related to drug-drug interactions and other interactions

5286 subjects received Menveo alone, while 899 received Menveo along with a concomitant vaccination. An additional 539 received Menveo 31 days after received a concomitant vaccination (Tdap, study V59P18).

Potential vaccine-vaccine interactions were evaluated in studies of MenACWY alone compared with MenACWY given with routine concomitant vaccines and of sequential administration of MenACWY given following Tdap. In the 11 to 18 year age group, MenACWY given with concomitant Tdap or with Tdap and HPV vaccine increased the incidence of reactions such as myalgia, arthralgia and malaise, which was reflective of the inherent reactogenicity of each of the vaccines administered. There was no evidence in the present investigations of vaccine-vaccine interactions when MenACWY was given concomitant with Tdap or with Tdap and HPV. There was also no evidence of vaccine-vaccine interaction when MenACWY was given 1 month after Tdap.

However, in study V59P18, there are different tabulated values of reactogenicity after concomitant vaccination with MenACWY, Boostrix and Gardasil. According to the clinical study report for V59P18, the frequency of “any reaction” (local, systemic, other) is 89% and local reaction is 85 % after concomitant vaccination with MenACWY, Boostrix and Gardasil. In “Integrated Summary of Clinical Safety” report, the frequency of “any reaction” is 75% and local reaction is 54% after concomitant vaccination with MenACWY, Boostrix and Gardasil. The Applicant explained that the different rates of reactions after concomitant vaccination are due to differences in the measurement, in one case, reactions to Menveo only were detected, while in the other case reactions to all vaccines were recorded.

- Discontinuation due to adverse events

One serious adverse event from study V59P18 (hypophyseal adenoma) led to withdrawal of the subject from the study, this event was judged not to be related to study vaccine.

- Post marketing experience

Not applicable.

- Discussion on clinical safety

MenACWY was well tolerated by the 6185 subjects aged 11-55 years that were included in five clinical studies. The reactogenicity profile of MenACWY was comparable to that of Menactra. Although a large proportion reported pain (41% versus 46%), only very few reported severe pain (2% versus 2%). The levels of pain following vaccination are similar to what is seen with other vaccines in adults. Systemic reactions following vaccination were generally low and comparable for the two vaccines. A relatively large proportion reported headache (30% versus 28%), though few reported severe headache (3% versus 2%). Headache in $\geq 10\%$ of subjects has been reported for other meningococcal vaccines, but also for DTaP vaccines as Boostrix/Infanrix and for Hepatitis A vaccines (Epaxal).

In all clinical studies individuals who had been exposed to meningococcal vaccines in the past were excluded. As this group might be revaccinated with MenACWY the Applicant has committed to present plans for further testing of immunogenicity and safety in this population, especially in persons who previously received a monovalent (conjugate) MenC vaccine and persons who have previously been vaccinated with a polysaccharide MenACWY vaccine.

Based on the limited information provided in pregnant women, the MAA has proposed a pregnancy registry involving two complementary methodologies. Two signal detection approaches will be employed in tandem, one using a prospective cohort methodology and the second using a case/control design. The applicant has committed to submit study protocols, including (among others) sample size calculations and study milestones.

The lack of data in elderly has been addressed in the RMP and the SPC has been updated accordingly. The MAA has committed to present safety data stratified by age in future PSURs.

The risk of vaccine failure is an important risk with most vaccines and has been included in the list of potential risks.

As the MAA applied for a paediatric investigation plan (PIP) according to EU regulation 1901/2006, the agreed studies in this PIP and hence the milestones and objectives of this development have been included in the EU-RMP.

2.5 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 MAA submitted a risk management plan.

Summary of the risk management plan:

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Identified risks:	Not applicable	Not applicable
Important potential risks		
Guillain-Barré Syndrome	Enhanced pharmacovigilance	Not applicable
Acute disseminated encephalomyelitis	Enhanced pharmacovigilance	Not applicable
Anaphylactic reactions	Routine pharmacovigilance	SPC section 4.3 provides a warning that individuals who are hypersensitive to any component of the vaccine should not be vaccinated
Thrombocytopenia	Routine pharmacovigilance	SPC section 4.4 notes that individuals with thrombocytopenia or other bleeding diatheses could be at increased risk of complications from an intramuscular injection
Vasculitis	Routine pharmacovigilance	Not applicable
Whole limb swelling	Routine pharmacovigilance	Not applicable
Brachial neuritis	Routine pharmacovigilance	Not applicable
Injection site reactions (severe)	Routine pharmacovigilance	Not applicable
Systemic reactions (severe)	Routine pharmacovigilance	Not applicable
Vaccine failure	Enhanced pharmacovigilance	Not applicable
Important missing information		
Safety of vaccine during pregnancy or lactation	Pregnancy registry	SPC section 4.6 declares that there are limited data on Menveo's use in pregnant or lactating women
Off label use in pediatric or elderly populations	Routine pharmacovigilance	SPC section 4.2 notes that there are insufficient data on these populations
Exposure to repeated doses, including booster responses	Routine pharmacovigilance	SPC section 4.2 states the need for, and timing of, a booster dose of Menveo has not yet been determined
Safety of vaccines in children < 11 years	Pediatric Investigation Plan (PIP)	SPC section 4.2 notes that there are insufficient data on children < 11 years
Safety of vaccine during pregnancy or lactation	Pregnancy registry	SPC section 4.6 declares that there are limited data on Menveo's use in pregnant or lactating women
Off label use in pediatric or elderly populations	Routine pharmacovigilance	SPC section 4.2 notes that there are insufficient data on these populations
Exposure to repeated doses, including booster responses	Routine pharmacovigilance	SPC section 4.2 states the need for, and timing of, a booster dose of Menveo has not yet been determined
Safety of vaccines in children < 11 years	Pediatric Investigation Plan (PIP)	SPC section 4.2 notes that there are insufficient data on children < 11 years

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The dossier covers the process intermediates (CRM197, MenA, MenC, MenW, Men Y polysaccharides and the Men-CRM conjugates), the lyophilised MenA conjugate component and the MenCWY liquid conjugate component as finished products.

The Applicant detailed the manufacturing processes. Overall, the production of all polysaccharides, CRM and Men-CRM conjugates is consistent. The analytical control procedures are summarised and the acceptance criteria and validation results are reported. The manufacturing process for purified polysaccharides is acceptably controlled and has been validated.

During the evaluation procedure a major objection was raised. The major objection was related to the alert limits for bioburden and the extremely high bioburden levels observed during validation of the drug substance. Satisfactory response was provided. The Company has also committed to provide additional information post-approval as defined in the follow-up measures. The shelf life for MenCWY Liquid and MenA Lyo of 24 months when stored at 2-8 °C is accepted.

In conclusion, the benefit/risk ratio was found positive with regard to the quality of the product.

Non-clinical pharmacology and toxicology

The program for non-clinical pharmacology is limited to immunogenicity data in mice and rabbits using ELISA and serum bactericidal assay. The mouse immunogenicity data are not relevant as all studies have been carried with inclusion of an adjuvant. The rabbit data indicate that the intended formulation of MenACWY is able to induce an antibody response to all antigens, which is also associated with serum-bactericidal activity. No important safety concerns were identified.

Efficacy

Throughout the studies submitted by the Applicant, MenACWY induced an immune response in adolescents (11 years and older) and adults leading to (short term) seroprotection against invasive disease caused by *Neisseria meningitidis* serogroups A, C, W135 and Y as defined by a hSBA titre of >1:8. For the main immunogenicity study (V59P13) this was achieved in 72%, 83%, 95% and 85% of subjects for A, C, W135 and Y respectively (% subjects with hSBA \geq 1:8). In the supportive studies, similar percentages of vaccinees achieved hSBA titres \geq 1:8 one month after vaccination.

The immune response to Menveo one month after vaccination was similar (for W and Y) or better (for A and C) as compared to the immune response to a plain polysaccharide MenACWY vaccine. Additionally, non-inferiority to the immune response of another protein conjugated MenACWY vaccine was shown. Moreover, there is no evidence that concomitant administration of Menveo with Tdap and HPV vaccine affects the short term immune response to the Men A, C, W, or Y antigens.

Safety

MenACWY was associated with a range of local and systemic adverse reactions commonly seen for vaccines, such as pain, erythema and induration, headache, myalgia, chills, and malaise. These adverse events were rarely severe. Concomitant administration with Tdap & HPV resulted in a slight increase in reactogenicity as expected. Overall, the safety profile, which was determined in over 6000 persons, does not preclude the use of MenACWY in adolescents (11-18 years) and adults (19-55 years).

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

The applicant provided a bridging document to indicate the similarities and differences between the PL for Menjugate and the PL for Menveo. Their patient information leaflets are very similar, therefore the company, as detailed in the *Guideline concerning consultation with target patient groups for the package leaflet product*, for Menveo references to the Menjugate user testing. This was judged acceptable.

Risk-benefit assessment

Benefits

MenACWY was shown to induce an immune response in adolescents (11 years and older) and adults leading to (short term) seroprotection against invasive disease caused by *Neisseria meningitidis* serogroups A, C, W135 and Y. These are part of the five serogroups (A, B, C, Y and W135) responsible for the vast majority of cases of meningococcal disease worldwide.

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 lack of hypo-responsiveness of MenACWY was demonstrated in study V59P1E1 where a challenge with plain polysaccharide vaccine was applied, and in study V59P7 where two doses of MenACWY was applied to toddlers 12-35 months.

An impact of MenACWY on pharyngeal carriage on meningococcal bacteria has not been investigated, but is supposed to be a benefit of conjugated meningococcal vaccines.

Risks

Considering the age limit in the currently sought indication, the data suggest that this vaccine is mainly suitable for persons travelling to areas where meningococcal disease occurs due to other serogroups than prevalent in their own countries. Hence, for the European situation, protection against mainly A, but also W135 and Y are most essential. MenC is more prevalent in the EU, and in several countries part of the childhood immunization programme.

However further data should be generated in order to document the effect of a repeated dose/booster dose in the age group covered by the indication for use. Such data should also include the potential for increased side effects due to repeated vaccination.

Furthermore there was evidence suggesting a negative effect of concomitant administration of Tdap with Menveo on the immune response to the pertussis antigens. The clinical relevance of this effect is presently unknown. A drop in the antidiphtheria Elisa GMC seen one month following vaccination with Tdap compared to baseline was explained by an initial response to the Menveo CRM carrier protein. Similarly, there is evidence suggesting a negative effect on the response to the W135 antigen when Menveo is administered one month after administration of Tdap.

It has also to be noted that there is limited data for use in subjects aged 56-65 years and no data in individuals aged > 65 years old.

Balance

The currently available immunogenicity data with regard to short term (one month) and long term (> 12 / 21 months) protection in subjects aged 11 years and above, can be considered sufficient to support

approval of a vaccine intended for subjects (from 11 years of age) at risk of exposure to *Neisseria meningitidis* serogroups A, C, W135 and Y. Although further persistence data should be generated in order to document whether a booster dose is needed. Furthermore the safety data available do not preclude the use of the vaccine.

From a clinical point of view the B/R of Menveo is positive for the proposed indication as the outstanding issues have been addressed appropriately and the SPC has been adapted accordingly.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Menveo for the “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.” was favourable and therefore recommended the granting of the marketing authorisation.

Furthermore, the CHMP takes note that the agreed Paediatric Investigation Plan is not fully completed yet as only some of the measures are completed. The CHMP reviewed the already available paediatric data of studies subject to this plan and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.