EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 November 2012
EMA/790069/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Bexsero

Common name: **Meningococcal group B Vaccine (rDNA, component, adsorbed)**

Procedure No. **EMEA/H/C/002333**

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

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Product information

Name of the medicinal product:	Bexsero
Applicant:	Novartis Vaccines and Diagnostics S.r.l. Via Fiorentina, 1 IT-53100 Siena Italy
Active substance:	-Recombinant *Neisseria meningitidis* group B NHBA fusion protein -Recombinant *Neisseria meningitidis* group B NadA protein -Recombinant *Neisseria meningitidis* group B fHbp fusion protein -Outer membrane vesicles (OMV) from *Neisseria meningitidis* group B strain NZ98/254 measured as amount of total protein containing the PorA P1.4
Common Name:	Meningococcal group B Vaccine (rDNA, component, adsorbed)
Pharmaco-therapeutic group (ATC Code):	Meningococcal vaccines (J07AH09)
Therapeutic indication:	Bexsero is indicated for active immunisation of individuals from 2 months of age and older against invasive meningococcal disease caused by *Neisseria meningitidis* group B. The impact of invasive disease in different age groups as well as the variability of antigen epidemiology for group B strains in different geographical areas should be considered when vaccinating. See section 5.1 for information on protection against specific group B strains. The use of this vaccine should be in accordance with official recommendations.
Pharmaceutical form:	Suspension for injection
Strengths:	One dose (0.5 ml) contains: -Recombinant *Neisseria meningitidis* group B NHBA fusion protein 50 micrograms

	-Recombinant *Neisseria meningitidis* group B NadA protein 50 micrograms -Recombinant *Neisseria meningitidis* group B fHbp fusion protein 50 micrograms -Outer membrane vesicles (OMV) from *Neisseria meningitidis* group B strain NZ98/254 measured as amount of total protein containing the PorA P1.4 25 micrograms
Route of administration:	Intramuscular use
Packaging:	pre-filled syringe (glass)
Package sizes:	1 pre-filled syringe with needle, 1 pre-filled syringe without needle, 10 pre-filled syringes with needle, 10 pre-filled syringes without needle

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List of abbreviations

CI	Confidence Interval
CSR	Clinical Study Report
DTPa-HBV-IPV/Hib	Infanrix Hexa™ (combined diphtheria and tetanus toxoids, acellular pertussis adsorbed, hepatitis B (recombinant), inactivated poliovirus, *Haemophilus influenzae* type b vaccine)
ECDC	European Centre for Disease Prevention and Control
ELISA	Enzyme Linked Immunosorbent Assay
EU	European Union
GCP	Good Clinical Practice
GMC	Geometric Mean Concentration
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
HHE	Hypotonic-hyporesponsive Episode
hSBA	Serum Bactericidal Assay using Human Complement
KD	Kawasaki Disease
LL	Lower Limit
MATS	Meningococcal Antigen Typing System
MedDRA	Medical Dictionary for Regulatory Activities
MenB	serogroup B meningococcus
MeNZB	Outer membrane vesicle vaccine derived from *Neisseria meningitidis* serogroup B strain NZ98/254. This vaccine was developed to combat the outbreak of group B meningococcal disease in New Zealand
MITT	Modified Intention to Treat
MMRV	Priorix Tetra™ (measles, mumps, rubella and varicella live-vaccine vaccine)
OMV	Outer Membrane Vesicles
OMV NZ	Outer membrane vesicle derived from *Neisseria meningitidis* serogroup B strain NZ98/254 (New Zealand strain)
OMV NW	Outer membrane vesicle derived from *Neisseria meningitidis* serogroup B strain H44/76 (Norwegian strain)
PCV7	Prevenar^{TM} pneumococcal vaccine (7-valent pneumococcal conjugate vaccine)
PP	Per Protocol
SBA	Serum Bactericidal Assay
SOC	System Organ Class
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novartis Vaccines and Diagnostics S.r.l. submitted on 7 January 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Bexsero, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication, active immunisation of individuals from 2 months of age and older against invasive meningococcal disease caused by *Neisseria meningitidis* group B. The impact of invasive disease in different age groups as well as the variability of antigen epidemiology for group B strains in different geographical areas should be considered when vaccinating. See section 5.1 for information on protection against specific group B strains. The use of this vaccine should be in accordance with official recommendations.

The legal basis for this application refers to:
Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is 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).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included EMA Decision P/038/2011 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-000139-PIP01-M01 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance Meningococcal group B vaccine contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP during the development phase (2006, 2007, 2008 and 2009). The Scientific Advices pertained to insert quality, non-clinical and clinical aspects of the dossier.

Licensing status

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

1.2. Steps taken for the assessment of the product

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

Rapporteur: **Kristina Dunder**

Co-Rapporteur: **Karsten Bruins Slot**

- The application was received by the EMA on 7 January 2011.
- The procedure started on 19 January 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 08 April 2011 The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 08 April 2011.
- During the meeting on 19 May 2011, 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 May 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 August 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 September 2011.
- During the CHMP meeting on October 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- During the CHMP meeting on January 2012, the CHMP agreed on the company's request for an extension of the submission of the responses to the list of outstanding issues.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 15 October 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding issues to all CHMP members on 9 November 2012.
- During the meeting on November 2012, 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 Bexsero on 15 November 2012.

2. Scientific discussion

2.1. Introduction

Invasive meningococcal disease occurs worldwide. Each year approximately 1.2 million cases of invasive meningococcal disease are recorded worldwide, of which 7,000 occur in Europe. The overall incidence in European countries ranges from approximately one to four cases per 100,000 population (ECDC surveillance report for 2007).

Infants are at the higher risk of acquiring the disease, followed by adolescents. In the older age groups the disease is extremely rare. In addition to age, another individual risk factor includes underlying immune deficiencies; the deficiency of complement components are known to determine infection. Crowding and concurrent upper respiratory tract infections might also contribute to acquiring the disease. Despite the availability of medical treatment and effective antibiotics, 8% of European patients die, increasing with age (ECDC surveillance report for 2007), and up to 11-19% of survivors have lifelong sequelae.

Over 90% of meningococcal meningitis and septicemia are caused by five of the 13 meningococcal serogroups, i.e., serogroups A, B, C, W-135 and Y. Serogroup B accounts for a high proportion of meningococcal disease cases in the Americas, Australia and Europe (74%, ECDC surveillance report for 2007).

The global incidence of serogroup B has been estimated between 20,000 and 80,000 cases per year, accounting for 2,000-8,000 deaths annually. In Europe, 3406 cases of serogroup B meningitis were reported in 2007. The incidence of disease due to serogroup B was highest in Ireland, the United Kingdom, Belgium and Spain. These same countries had early introduction of MCC vaccination after high incidences of serogroup C in the late 1990s (ECDC surveillance report for 2007 [2010]).

No broadly effective serogroup B meningococcal vaccines are available. Capsular polysaccharide vaccines have been used successfully in preventing disease and limiting epidemics and outbreaks caused by meningococcal serogroups A, C, W135, and Y.

However, the capsular polysaccharide of meningococcal serogroup B is poorly immunogenic in humans, possibly due to similarities in serogroup B carbohydrate moieties to carbohydrates widely distributed in the human body. As a result, research has focused on proteins in the outer membrane of meningococci as potential antigens for candidate vaccines. Serogroup B vaccines based on protein-containing outer membrane vesicles (OMV) have been safe and effective in controlling epidemic disease caused by strains homologous to the vaccine strain in Cuba, Brazil, Chile, Norway, and New Zealand. The use of these OMV vaccines to combat serogroup B meningococcal disease has been limited, however, due to the strain-specific nature of the protection and the lack of consistent efficacy in young children.

Bexsero is indicated for active immunization against invasive disease caused by *Neisseria meningitidis* serogroup B strains in individuals from 2 months of age and older. The efficacy of Bexsero against invasive meningococcal disease (IMD) has been inferred from the ability of the vaccine to induce functional bactericidal antibodies directed against serogroup B meningococci. Immunity to meningococcal disease is mediated primarily by serum antibodies that are specific for bacterial surface components, and are capable of activating complement once bound, resulting in bacteriolysis. Serum bactericidal activity has been accepted as a valid surrogate for predicting the clinical efficacy of serogroup B meningococcal vaccines. Functional bactericidal antibodies induced by vaccination with Bexsero will be measured by the Serum Bactericidal Assay.

The rMenB+OMV NZ vaccine has been developed using knowledge gained during vaccine development for the Norwegian (MenBvac) and New Zealand (MeNZB) epidemics, together with the identification of the *N. meningitidis* serogroup B genome sequence to develop an effective serogroup B vaccine. The availability of the bacterial genome sequence allowed identification of conserved surface-exposed outer membrane proteins of serogroup B strains that were targets for bactericidal antibodies.

The current vaccine formulation or the rMenB+OMV NZ vaccine is based on three proteins: i) factor H binding protein (fHbp), ii) Neisseria adhesin A (NadA) and iii) Neisserial Heparin Binding Antigen (NHBA) or 287. To increase the potency of the immune response and to facilitate large-scale vaccine manufacturing, the fHbp protein has been combined with the accessory protein GNA2091 (936), and the 287 protein has been combined with GNA1030 (953), to create two fusion proteins. In addition the vaccine also contains OMV derived from the New Zealand epidemic strain.

Type of application and other comments on the submitted dossier

The Marketing Authorisation Application (MAA) for Bexsero was submitted in accordance with Article 8.3 of Directive 2001/83/EC as a complete and independent application by Novartis Vaccines and Diagnostics S.r.l. The application is submitted under Article 3(1) of Regulation (EC) No 726/2004, i.e. the centralised procedure is mandatory (Biotech medicinal product).

In accordance with Regulation (EC) No 1901/2006, the applicant submitted in March 2008 an application for Paediatric Investigational Plan (PIP) for Multi-Component Meningococcal B Vaccine with a request of waiver in neonates/infants less than 8 weeks of age and deferral for some studies contained in the paediatric investigational plan as per final PDCO Opinion on the PIP application adopted on 21 May 2010. A partial compliance check was requested, but a final report was not available at the time of submission.

2.2. Quality aspects

2.2.1. Introduction

About the product

Bexsero is a Meningococcal B vaccine consisting of four drug substances, as follows:

- protein 961 c - a fragment of Neisseria adhesin A (NadA), a surface-exposed oligomeric protein belonging to the Oligomeric Coiled-coil Adhesin (OCA) family involved in binding to epithelial cells,

- protein 287-953 - a fusion protein product of protein 287 (Neisserial Heparin Binding Antigen or NHBA), a primary antigenic component, and protein 953, an accessory protein that enhances the immunogenicity of its fused counterpart and

- protein 936-741 - a fusion protein product of proteins 936 and 741 (Factor H Binding Protein or fHbp) where Protein 741 is the primary antigenic component while 936 is an accessory protein that enhances the immunogenicity of its fused counterpart.

- ***Outer membrane vesicles (OMV)*** from *Neisseria meningitidis*, group B strain NZ 98/254 (known as OMV).

The drug substances are adsorbed on aluminium hydroxide ($Al(OH)_3$) as a suspension for injection. The $Al(OH)_3$ concentration in Bexsero is 1.5 mg/ dose which corresponds to 0.5 mg of elemental aluminium per vaccine dose.

Composition of Bexsero Vaccine

Component	Quantity per 0.5 mL dose
rp287-953	50 µg
rp961c	50 µg
rp936-741	50 µg
OMV	25 µg
Excipients	
Aluminium hydroxide	1.5 mg[1]
Sodium chloride	3.125 mg
Sucrose	10 mg
Histidine	0.776 mg
Water for Injection	up to 0.5 mL

[1] Aluminium hydroxide 1.5 mg corresponds to 0.5 mg of elemental aluminium.

2.2.2. Active Substance

Bexsero contains 4 different active ingredients, Outer Membrane Vesicles (OMV) which are extracted via detergent from the bacterial membrane of *Neisseria meningitidis* (*N. meningitidis*) serogroup B strain NZ98/254 and three *N. meningitidis* cell surface antigen; Protein 961c, Protein 287-953, Protein 936-741, which are produced in *E.coli* by recombinant DNA technology.

Many of the issues mentioned below are common to the different antigens and the finished product.

Manufacture

OUTER MEMBRANE VESICLES (OMV)

Outer Membrane Vesicles (OMV) are extracted via detergent from the bacterial membrane of Neisseria meningitidis (*N. meningitidis*) serogroup B strain NZ98/254. The primary immunogenic components of the OMV are the outer membrane proteins (OMPs) and the membrane-bound lipopolysaccharides (LPS). As OMVs are complex mixtures of lipids, OMPs, and peri-plasmic components, structural descriptions is limited to those that are likely related to the mode of action, namely the major OMP antigens and LPS.

The major outer membrane proteins (OMPs) of *N. meningitidis* have been designated Class 1 (PorA, Serotype P1.4) through Class 5 (Opa). The Class 1, 2, and 3 proteins are porins that show significant antigenic variation. All meningococcal strains carry either Class 2 (PorB2) or Class 3 (Por B3) protein. These proteins function as anion-selective porins and probably occur in the outer membrane as trimers.

A Class 4 OMP, also called Rmp (Reduction-modifiable protein) due to its shift in mobility in SDS-PAGE after reduction, is closely related to protein III (PIII) of *N. gonorrhoeae*. The Class 4/RmpM OMP is constitutively expressed, is antigenically invariable, and is closely associated with the porin molecules, acting as a stabilizer.

The Class 5 protein, Opc, is a surface-exposed protein forming trimers or tetramers in the outer membrane.

The *N. meningitidis* outer membrane is an asymmetric bi-layer that consists of phospholipids on the inner leaflet and the lipid anchor region of lipopolysaccharides (LPS), lipid A, on the outer leaflet.

Meningococcal LPS is structurally distinct from those of enteric Gram-negative bacilli. It lacks the O-antigen repeat present in enteric bacteria, but the core LPS molecule is heterogeneous both within and between strains and has been classified into 12 distinct immunotypes (L1-L12) on the basis of monoclonal antibody reactivity. OMV NZ vaccine contains both the L1 and L3 immunotypes.

One-dimensional SDS-PAGE of OMV vaccines generally reveals between 20-30 proteins, with estimated molecular weights from 22,800 to 89,100 Da. Among these are the highly expressed porin proteins (PorA and PorB), the Class 4 and 5 antigens and other major antigens, including Omp85, FetA (Class 1, previously referred to as FrpB), and NspA (Class 3).

Production and control of starting materials/intermediates

Working seeds of *Neisseria meningitidis* serogroup B strain NZ98/254 are used to prepare an inoculum. The culture is expanded through serial fermentation steps. After fermentation the bacterial suspension is concentrated by ultrafiltration and inactivated using a detergent solution. The inactivated suspension undergoes centrifugation and the supernatant is recovered to yield the crude OMV intermediate that is purified through a concentration and diafiltration step and ultracentrifugation.Finally the filtered pre-bulk is sterile filtered to yield the OMV sterile bulk concentrate.

The OMV bulk is stored at 2-8°C.

Sufficient information has been provided and the production of OMV is considered adequate.

Seed banking system, characterisation and testing

The seed strain *Neisseria meningitidis (N. meningitidis*) serogroup B, strain NZ 98/254 is a wild type strain. The strain was selected for its good yield in production and because it was representative of the circulating *N. meningitidis* serogroup B strain responsible for an epidemic in New Zealand. The establishment and testing of the seed lot system is considered acceptably described.

The testing of the specifications on the Master and Working Seed is the same. The testing is in line with the Ph. Eur monograph for Meningococcal vaccines.

Process validation

Changes performed during the manufacturing development have been specified and data submitted to support the comparability of the products.

Characterisation

The OMV contains a multitude of proteins (>40). The applicant has standardized the major outer membrane proteins including Class 1 (PorA). These are quantified by SDS-PAGE.

Specifications for OMV concentrated bulk

The company releases the OMV sterile bulk concentrate based upon purity, protein pattern, protein concentration, identity, appearance, pH, endotoxin, DNA content, process related impurities, lipopolysaccharides, sucrose and sterility.

The specifications applied are those recommended by general Ph. Eur monographs and also internal specifications.

Analytical methods have been adequately described and validated.

Batch analysis

Batch analysis data for all lots were compared. Data from batches demonstrate a consistent production process. The specifications from the batches presented are also met.

Reference standard

An internal reference standard, used to determine the purity of OMV components via SDS-PAGE, is a released lot of OMV concentrated bulk. For qualification, the new reference standard is tested against the previous standard. For each standard, the molecular weight bands must be clearly separated, show similar electrophoresis patterns and the new reference standard must meet the requirements of the product specification for OMV components.

The quality of the reference standard and its relevance for its intended purpose is described in detail as the process to qualify a new standard.

Container closure system

The closure system is of pharmaceutical grade. The compatibility between the OMV bulk and primary container/closure materials is demonstrated through stability studies.

Stability

The stability studies were conducted at two temperatures. Long-term stability studies were performed at the recommended storage temperature for the claimed shelf life. Accelerated studies were performed to generate additional information on the thermal stability profile of the drug substance.

Recombinant protein 961, 287-953 and 936-741

General description

The recombinant antigens are similar in their production and are developed through “reverse vaccinology”. The first step in this process was the completion of the genome sequence of the pathogen of interest. Several algorithms were used to identify putative cell-surface or secreted proteins that could potentially elicit antibody responses in a human host. For Meningococci of serogroup B, several hundred of potential vaccine candidates were identified by bioinformatics approaches. The next step in the process was to produce recombinant proteins in *Escherichia coli*, have these purified and used as immunogens in mice. Immune sera were collected and assayed for their ability to bind to the surface of MenB cells and for their bactericidal activity in vitro. Proteins that had high titres in all of the assays were taken into the final stage of evaluation, which assessed the extent of protein sequence variability in these proteins across large numbers of MenB isolates. From this large-scale screening process, three new vaccine candidates emerged that met all of the criteria.

Structure for Recombinant protein 961

Protein 961c is a fragment of Neisseria adhesin A (NadA), a surface-exposed oligomeric protein belonging to the Oligomeric Coiled-coil Adhesin (OCA) family. NadA is a meningococcal adhesin molecule involved in binding to epithelial cells. The protein derives from *Neisseria meningitidis* (*N. meningitidis*) serogroup B Strain 2996. This protein is also identified in the literature as Genome-derived Antigen (GNA) 1994 (or NMB1994), based on the reverse vaccinology approach that allowed its identification. The 961c antigen is expressed via bacterial fermentation by standard recombinant DNA technology methods in *Escherichia coli* (*E. coli*) using a plasmid vector system.

Structure for Recombinant protein 287-953

Protein 287-953 is a fusion protein product of 287 (Neisserial Heparin Binding Antigen or NHBA), a primary antigenic component, and 953, an accessory protein that enhances the immunogenicity of its fused counterpart. In nature, NHBA is expressed on the *Neisseria meningitidis* (*N. meningitidis*) cell surface. NHBA is able to bind heparin, and heparan sulphate. The binding to heparin is associated with an increased resistance to the killing activity of normal human sera.

Protein 287 is derived from *N. meningitidis* serogroup B Strain NZ98/254 (also referred to as 394/98) and Protein 953 is derived from serogroup B Strain 2996. Proteins 287 and 953 are also identified in the literature as Genome-derived Antigens GNA2132 (or NMB2132) and GNA1030 (or NMB1030), respectively, based on genome mining or the reverse vaccinology approach. The fusion protein is expressed via bacterial fermentation by standard recombinant DNA technology methods in *Escherichia coli* (*E. coli*) using a plasmid vector system.

Structure for Recombinant protein 936-741

Protein 936-741 is a fusion protein product of 936 and 741 (Factor H Binding Protein or fHbp). Protein 741 is the primary antigenic component while 936 is an accessory protein that enhances the immunogenicity of its fused counterpart. In nature, the Factor H Binding Protein (741) is widely expressed on the *Neisseria meningitidis* (*N. meningitidis*) cell surface and binds to human factor H, a 150 kDa inhibitor of the alternative complement pathway (an innate component of the immune system's natural defense against infection that is not B- or T-cell mediated). The binding of factor H enhances the ability of N. meningitidis to resist complement-mediated killing, thereby providing an effective strategy to evade host defense mechanisms. Antibodies directed against fHbp can mediate serum bactericidal activity (e.g. direct bacteriolysis via the complement classical pathway) but also can block binding of fH increasing the susceptibility to killing by the complement alternative pathway.

Protein 936 is derived from *N. meningitidis* serogroup B Strain 2996 and Protein 741 from serogroup B Strain MC58. Proteins 936 and 741 are also identified in the literature as Genome-derived Antigens GNA 2091 (or NMB2091) and GNA 1870 (or NMB1870), respectively, based on genome mining or the reverse vaccinology approach. The fusion protein is expressed via bacterial fermentation by standard recombinant DNA technology methods in *Escherichia coli* (*E. coli*) using a plasmid vector system.

Production process

The production process is similar for the three components: The antigens are produced separately. Working seeds of *E. coli* containing the plasmid coding for the respective protein are used to prepare an inoculum. During the fermentation step, *E. coli* cells are expanded, the recombinant protein 961c is

expressed and secreted into the supernatant, whilst the other two recombinant proteins 287-953 and 936-741 are expressed intracellularly, and harvested. After the broth has been harvested, the recombinant protein is separated (isolated) from the bacteria via centrifugation and filtration steps. The last series of steps in bulk manufacture are the purification steps in which the recombinant protein is passed through a series of chromatography columns and filtered. The expression construct for all three antigens uses the same host cell, the genetic construct was to the greatest extent adequately described in the initial submission.

No starting material of animal or human origin is used during the inoculation preparation or fermentation of the active pharmaceutical ingredient (API). As regards the control strategy this was considered adequately described.

The testing of the WCB and the acceptance criteria is the same as for the MCB except on the absence of test for plasmid structural stability, plasmid sequence and bacteriophages.

The production and control of the 961c, 287-953 and 936-741 is adequately described.

Process development

Some changes are made from phase I/II to phase III and no significant changes between phase III and the commercial production. Comparable data from these lots have been presented and considered acceptable.

Characterisation

In addition to the routine QC testing, characterisation was conducted on the protein bulks including amino acid sequencing, experimental molecular mass analysis by direct infusion in electrospray quadrupole ESI-q-Tof mass spectrometer. SDS-PAGE analysis under reducing conditions is used to determine purity and integrity of bulk protein. Size exclusion-High Performance liquid chromatography (SE-HPLC) method is used to determine purity. SBA protein concentration is used for quantification of total protein for in –process controls, release and stability testing. Western blot is used for confirmation of the identity. HCP ELISA is used for quantification of residual HCP. The results provided confirmed the appropriateness of the analytical methods.

Specifications

The release specifications for the bulk recombinant proteins include: purity, protein content, identity, HCP, osmolality, endotoxin, bioburden, pH, conductivity, DNA, and process related impurities.

The tests and specifications comply with the Ph. Eur requirements. Appropriate validation for internal tests has been provided.

Validation of the methods has been carried out according to applicable ICH guidelines and is considered acceptable.

The presented batch analysis data shows an acceptable consistency in production.

Reference standard

Reference standards are representative for batches used in the clinical studies. Satisfactorily verification has been provided.

Container closure system

The closure system is of pharmaceutical grade. The compatibility between the bulk concentrate recombinant proteins and primary container/closure materials is demonstrated through stability studies.

Stability

All three bulks are stable under the recommended conditions for the claimed shelf-life.

2.2.3. Finished Medicinal Product

Bexsero is a suspension for injection in pre-filled syringe (PFS) and contains three recombinant proteins (rp), Outer Membrane Vesicles (OMV), and excipients (sodium chloride, histidine, sucrose, aluminium hydroxide and water for injection).

The vaccine is supplied in a 1-mL hydrolytic glass pre-filled syringe without a pre-affixed needle. Syringes are sealed with a bromobutyl rubber plunger stopper and tip cap.

Pharmaceutical Development

Bexsero consists of three recombinant proteins and Outer Membrane Vesicles, in 10mM histidine buffer, 6.25 mg/mL sodium chloride, pH 6.5, with 3% sucrose solution and aluminium hydroxide at 0.5 mg/ 0.5 mL aluminium.

The histidine buffer was used to adjust pH of the drug product, assuring antigen adsorption and product stability. Sodium chloride and sucrose solution were added to obtain an isotonic preparation. Aluminium hydroxide was added as adjuvant/adsorbant to enhance immunogenicity. In Bexsero vaccine, aluminium hydroxide concentration was selected to achieve adequate adsorption of all antigens. This concentration corresponds to 0.5 mg/dose (0.5 mL) of elemental aluminium, which is within the allowable dose of aluminium for human vaccines as per Ph. Eur.

The constiuents of the product and their concentration have been adequately justified.

Some changes were made in the composition from phase II to phase III. The differences include changes to the concentrations of sodium chloride and sucrose. No changes in composition occurred between phase III and the commercial composition.

There are no overages used in the manufacture of this vaccine.

An overfill of 0.1 mL is included in the syringe to ensure that 0.5 mL can be withdrawn.

Manufacture of the product

The manufacturing process for the drug product involves formulation of the drug substances with Aluminium Hydroxide and buffers, followed by aseptic filling, visual inspection and packaging.

A thorough validation program has been performed and shows that the process is under control.

Product specification

The release and stability tests and specifications for Bexero vaccine includes test for aluminium content, degree of adsorption as well as other compendial tests (sterility, endotoxins, pyrogens etc.). Consistency of batches is assured by the implementation of an in vivo immunogenicity test in mice.

The sensitivity and the proposed specifications of the assay were part of a major objection during the assessment process.

The applicant made a thorough work to develop a new bioassay which is more sensitive. A format in mice with injection of multiple dilutions of the test sample and a comparison with a clinically qualified reference standard was presented and was considered acceptable.

The applicant proposed specifications at release and at the end of shelf-life for the improved in vivo immunogenicity assay in mice. The specifications are acceptable and are based on non-inferiority of the tested lot to a clinically qualified reference standard.

The proposed acceptance criteria applies both to release and end of shelf-life (proposed 24 months).

Another major objection was related to the test for pyrogens. Prior to injection into rabbits the product was diluted to an extent which was not considered in line with conditions accepted for single component OMV vaccines previously used in Norway and New Zealand. Thus, the Applicant was asked to provide additional data to verify the sensitivity of the test for pyrogens. The applicant responded to these concerns and was able to use the same dilution as the New Zealand vaccine. Further measures were introduced to minimise the risk for false positives in the assay. The applicant was able to demonstrate that the method used is of sufficient robustness and sensitivity.

Concern over endotoxin assay variability was solved and measures introduced considered acceptable.

The release tests for the final containers include the following: identity, volume, appearance, aluminium hydroxide test, pH, osmolality, endotoxin, adsorption rate, sterility, pyrogen, in-vivo immunogenicity test. Release specifications are accepted. Analytical methods have been adequately described and validated.

Stability of the product

The proposed shelf-life of the final product is 24 months, when stored at 2-8°C, protected from light. To support the current shelf-life, stability studies were initiated on three full-scale consecutive final product lots used for Phase III clinical trials; these lots also served as consistency lots for the manufacturing process. Tested batches showed stable results except the initial results showed for most batches a decrease in immunogenicity using the original method. As mentioned above, during the evaluation of the submission it was highlighted that the initial immunogenicity assay of limited sensitivity and a new assay has been introduced. This means that no stability data were present to support the shelf life using the currently proposed methodologies.

In the absence of real time stability data generated with the new assay, the Company initiated testing of a number of lots of Bexsero in the new in vivo immunogenicity assay. Data indicate that lots of Bexsero used in clinical trials meet the proposed specifications for the new in vivo immunogenicity assay . These data, from lots that were beyond the proposed shelf life at the time of testing, supports that the proposed shelf-life of 24 months for Bexsero, when stored at 2-8°C and protected from light. As mentioned below, this will be further supported by real time stability data. Taking this into consideration, it was deemed that sufficient data were presented supporting this shelf life even without actual real time data as these are not available using the new in vivo immunogencitiy method.

Further actions to ensure that vaccine lots released onto the market will remain within specification throughout the claimed shelf life were agreed.

Adventitious agents

The facilities and equipment as well as the adventitious agents safety evaluation has been acceptably addressed.

GMP

Acceptable GMP status has been verified for the involved manufacturers.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The chemical/pharmaceutical part of the Bexsero dossier is of acceptable standard. During the assessment process, three major objections were identified related to the lack of clinical qualification of specifications for important attributes (protein purity of recombinant antigens, protein pattern of the OMV component and immunogenicity) of the drug product, indications of lack of comparability between OMV bulks produced at different sites and the test for pyrogens which was not considered adequate. Data have been provided to support the specifications for the protein purity/ protein pattern and following submission of additional data it was verified that the production at the two sites resulted in comparable products. The applicant has made a thorough work to improve the format of the bioassay and also to improve the pyrogen and endotoxin assays. The vaccine is inherently pyrogenic due to its nature but the applicant has succeeded to lower the variability of the endotoxin assay and also minimized the number of false positives of the pyrogen assay and increased the sensitivity of the assay. The format of the potency assay and the acceptance criteria has been sufficiently justified. No real time stability data covering the proposed 24 months with the improved assay is presented but the applicant has through analysis of retained samples of aged material acceptably supported their claim. All the major objections have been satisfactorily addressed by the applicant.

In addition, all other concerns raised during the assessment have been acceptably resolved. A number of recommendations for revision of specifications etc. when more experience is gained or tests to be introduced have been made. These are not considered critical to the overall quality of the product and hence a positive opinion can still be recommended.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The applicant has acceptably resolved all issues identified during the assessment and there are no remaining quality issues preventing a positive opinion.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1.	The applicant is recommended to use the improved bioassay method to confirm stability data according to ICH requirements. If necessary, shelf-life specification limits should be revised.
2.	The Applicant is recommended to introduce in the release specification a validated test to confirm the vesicular size/nature of the OMV component.
3.	The applicant is recommended pending the positive outcome of the development studies to complete the validation of the improved formulation process with an in-line filtration process including characterization, comparability, aseptic confirmation and minimum number of months of stability.
4.	The applicant is recommended to re-evaluate intermediate bioburden limits of the rp961c downstream process after accumulating in-process data from sufficient number of purification batches.
5.	The Applicant is recommended to use smaller peptide tolerance windows for future comparative studies using Mass spectroscopy after process changes etc. to identify eventual differences in levels of post-translational modified forms.
6.	The applicant is recommended to set a release specification for the rp287-953 Ox-Red ratio, as determined by RP-HPLC, once results from sufficient number of batches are available.
7.	The Applicant is recommended to improve their adsorption rate method. If the modified method improves the analysis, the new assay should be validated and implemented.

2.3. Non-clinical aspects

2.3.1. Introduction

Bexsero is indicated for active immunization against invasive disease caused by *Neisseria meningitidis* serogroup B strains of individuals from 2 months of age and older.

2.3.2. Pharmacology

The Bexsero vaccine is a mixture of two protein-protein fusion antigens (287-953 and 936-741, where 287 and 741 are the primary antigen components and 953 and 936 are present as accessory protein), one single antigen (961c) and OMV NZ, formulated with an aluminium hydroxide [$Al(OH)_3$] adjuvant. The sequences for these antigens are derived from three *Neisseria meningitidis* serogroup B strains; antigen 287 is derived from strain NZ98/254; antigens 953, 936, and 961c are derived from strain 2996; and antigen 741 is derived from strain NC58. The OMV component is a suspension that consists of small, membranous spherical vesicles in which the native complex antigen composition of the sub-capsular cell surface of *N. meningitidis* serogroup B strain NZ98/254 (B:4:P1.7-2,4) is highly preserved. As a result, the OMV contain the most abundant proteins of the outer membrane (PorA and PorB are the main components), some minor proteins, and small amounts of lipopolysaccharide (LPS).

Non-GLP methods were developed for assessment of immunogenicity in studies in mice, Guinea pigs, rabbits, and non-human primates (antibody titres by ELISA and antibody function by SBA). The non-GLP status of the ELISA and SBA assays used to evaluate the sera from the GLP rabbit studies is not considered to constitute a deficiency in the program because the purpose of these assays was not related to safety assessment. Immunogenicity was assessed in order to demonstrate that rabbits were an appropriate toxicology species that exhibits an immune response that is qualitatively similar to humans, that control rabbits did not receive test vaccine, and that treated rabbits did receive the test vaccine.

Primary pharmacodynamic studies

GLP and non-GLP studies have assessed the immunogenicity of individual antigenic components of Bexsero and of Bexsero itself. These studies were conducted in mice, Guinea pigs, rabbits and monkeys and were designed primarily to determine the generation of antibodies and induction of Serum Bacterial Activity (SBA) following single and repeated administrations of Bexsero at doses comparable to, or greater than, those indicated for clinical use. In addition, in a passive protection model, immune mouse antisera protected animals against development of bacteraemia caused by challenge with various serogroup B strains of *N. meningitidis*.

Secondary pharmacodynamic studies

Studies assessing secondary pharmacodynamics of Bexsero have not been conducted.

Safety pharmacology programme

Studies assessing safety pharmacology of Bexsero have not been conducted. However, no safety issues pertaining to the cardiovascular, central nervous and/or respiratory systems were identified in the nonclinical pharmacology and toxicology studies conducted with Bexsero based on standard observations. In the GLP toxicology studies conducted in rabbits, no changes in heart rate or

respiration rates and/or clinical observations indicative of central nervous system, cardiovascular or respiratory system effects were observed following administration of any of the vaccine formulations tested, including the clinical formulation of Bexsero.

Pharmacodynamic drug interactions

Studies assessing pharmacodynamic drug interactions with Bexsero have not been conducted.

2.3.3. Pharmacokinetics

Pharmacokinetic studies (absorption, distribution, metabolism, and excretion) have not been conducted with Bexsero. This is in accordance with applicable guidelines.

2.3.4. Toxicology

Single dose toxicity

A combined single dose toxicity and repeat dose toxicity study was performed in rabbits.

Repeat dose toxicity

In a GLP study, the local and systemic toxicities resulting from single and repeat IM doses of various rMenB vaccine formulations were assessed in New Zealand White rabbits.

Study groups were:

Group	Treatment	Dose
1	$Al(OH)_3$	1.5 mg $Al(OH)_3$
2	rMenB+OMV NW	50 µg each of 287-953, 961c and 936-741 + 25 µg OMV NW + 1.5 mg $Al(OH)_3$
3	rMenB+OMV NZ (Bexsero)	50 µg each of 287-953, 961c and 936-741 + 25 µg OMV NZ + 1.5 mg $Al(OH)_3$
4	rMenB	50 µg each of 287-953, 961c and 936-741 + 1.5 mg $Al(OH)_3$
5	rMenB (37ºC)	50 µg each of 287-953, 961c (stored at 37ºC) and 936-741 + 1.5 mg $Al(OH)_3$
6	2× rMenB+OMV NW	100 µg each of 287-953, 961c and 936-741 + 25 µg OMV NW + 3 mg $Al(OH)_3$

The group size was 8-10 male / female rabbits. The rabbits were immunized on Day 1, 15, 29, 43 and 57. One to two animals/groups were necropsied on Day 3 (two days after the first dose), one to two animals/group on Day 15 (just before the second dose), three animals/group on Day 59 (two days after the fifth dose) and three animals/group on Day 71 (14 days after the fifth dose).

The immunogenicity assessment is described in the section on Primary pharmacodynamics. In short, a weak immune response was observed after a single dose, while after two doses or more there was a strong immune response in all vaccine groups.

In the clinical pathology data, there were significant changes in the mean fibrinogen, leukocyte and neutrophil counts, and globulin values that were indicative of inflammation, and together with the changes observed in the mean creatinine kinase and lactate dehydrogenase values suggest skeletal muscle involvement (most likely at the injection sites). The vaccine formulations containing NW OMV or NZ OMV produced significantly higher mean fibrinogen, leukocyte and neutrophil counts. Although these changes were mild and transient; they are considered treatment-related effects. The remaining

significant changes that were observed were generally small in magnitude, had no biological significance, and/or were due to individual animal variation.

Genotoxicity

Studies assessing genotoxicity of Bexsero have not been conducted. This is in line with applicable guidelines.

Carcinogenicity

Studies assessing carcinogenicity of Bexsero have not been conducted. This is in line with applicable guidelines.

Reproduction Toxicity

Two GLP reproductive and developmental toxicity studies have been carried out with the 4CMenB vaccine. The first was a dose-range finding developmental study in rabbits, while the second study was a pivotal fertility, developmental and perinatal toxicity study with postnatal evaluation in rabbits.

Parameters evaluated during these studies included viability, clinical observations, skin reactions, body weights, food consumption, mating and fertility indices and gross lesions. Rabbits were also evaluated for reproductive parameters such as pregnancy status, gravid uterine weights, number and distribution of corpora lutea, implantation sites, and live and dead foetuses as well as early and late resorptions. All foetuses were sexed, weighed, and examined macroscopically for any external anomalies to detect any embryofoetal toxicity/teratogenicity. Blood samples for antibody (ELISA) and Serum Bactericidal Activity (SBA) analyses were collected from does and foetuses. The major findings are presented in Table 1.

Table 1: Summary of reproductive and developmental toxicity studies

Study ID	**Species/ Sex/Number/ Group**	**Dose/Route**	**Duration**	**Major findings**
UBA00041	Rabbit/ New Zealand White 6 females/group	*Group 1*: 0.9% Sodium Chloride *Group 2*: rMenB (50 µg each antigen) + 1.5 mg $Al(OH)_3$ *Group 3*: rMenB (50 µg each antigen) +25 µg OMV NZ + 1.5 mg $Al(OH)_3$ *Group 4*: rMenB (100 µg each antigen) + 3 mg $Al(OH)_3$ *Group 5*: rMenB (100 µg each antigen) +50 µg OMV NZ + 3 mg $Al(OH)_3$ Intramuscular administration	Dosing on days 1, 15, and 29 prior to mating and on Days 7 and 20 of gestation. Caesarean sectioning performed on day 29 of gestation.	Bexsero and rMenB were immunogenic and well tolerated. No evidence of reproductive or developmental toxicity was observed.

UBA00044	Rabbit/ New Zealand White 27 females/group	*Group 1 and 3*: 0.9% Sodium Chloride *Group 2 and 4*: rMenB (50 µg each antigen) + 25 µg OMV NZ + 1.5 mg $Al(OH)_3$ Intramuscular administration	Dosing on days 1, 15, and 29 prior to mating and on Days 7 and 20 of gestation *Group 1 and 2*: Caesarean sectioning performed on day 29 of gestation. *Group 3 and 4*: Natural delivery and necropsy with offspring on day 29 of lactation.	Bexsero and rMenB were immunogenic and well tolerated. No evidence of reproductive or developmental toxicity was observed.

Toxicokinetic data

Studies assessing Toxicokinetics of Bexsero have not been conducted. This is in line with applicable guidelines.

Local Tolerance

As part of the single and repeat dose toxicity study in rabbits, the local tolerance to single and repeat IM doses of various rMenB vaccine formulations was assessed in New Zealand White rabbits. The local reactogenicity of the vaccine formulations was generally of a low order of magnitude, and changes were slightly exacerbated compared to the $Al(OH)_3$ placebo formulation. Injection site inflammation was partially to fully reversible within the 14-day recovery period and was consistent with IM administration of an immunogenic $Al(OH)_3$-adjuvanted vaccine.

Other toxicity studies

2.3.5. Ecotoxicity / environmental risk assessment

According to the Guideline on the Environmental Risk Assessment (ERA) of Medicinal Products for Human Use, an ERA is not required.

2.3.6. Discussion on non-clinical aspects

A combined single-dose and repeat-dose toxicity study was performed in rabbits. Rabbits were given up to five doses of the vaccine, at a full human dose or double the human dose. There were no important toxicological findings. There were transient changes in fibrinogen and in neutrophil and leukocyte counts. These changes are likely to be directly related to the immunostimulatory activity of the vaccine. Vaccine formulations lacking the OMV component induced less change in these parameters. This suggested that the OMV component may act partly as an adjuvant (possibly mediated by LPS), thereby enhancing the immune response.

There were no studies on genotoxicity and carcinogenicity, which is in line with applicable guidelines.

A reproductive and developmental toxicity study was performed in rabbits. Five human doses were given during the pre-mating (3 doses) and gestation (two doses) periods. Rabbits were evaluated by caesarean section at gestation day 29 or were allowed to deliver naturally and were assessed at lactation day 29. There was an increased incidence of skeletal variations in rabbits given the vaccine,

and there was a statistically significant reduction in the average number of ossified forelimb phalanges. In the study, there was only one case of malformation (one foetus in the control group with interventricular septal defect in the heart and persistent truncus arteriosus). The statistically significant difference in ossification sites in forelimb phalanges was minimal and unlikely to be of relevance (13.95 vs. 13.72), and there were no other reductions in ossification site averages. The design of the study, with a single dose level of Bexsero, somewhat limits the possibility of detecting developmental toxicity.

In conclusion, the data do not suggest a risk for negative effects of the vaccine on human reproductive and developmental functions.

A number of in vitro studies were performed to assess potential effects of rMenB protein antigens on cytotoxicity, cell monolayer permeability, cytokine induction, and cell activation. These studies demonstrated binding of rMenB protein antigens and the OMV component to endothelial cells but there was no evidence of toxicity. The rMenB protein antigens induced cytokine production similarly to other licensed vaccines. The in vitro activity of the OMV component was similar to that of LPS, a constituent of OMV.

Overall, the non-clinical package is adequate to support this application and there are no non-clinical outstanding concerns to object to the approval of Bexsero.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical program adequately supports the marketing authorisation application for Bexsero. The toxicity profile of Bexsero is sufficiently characterised by the non-clinical data submitted. The statement in section 5.3 of the SmPC pertaining to non clinical data is appropriate.

2.4. Clinical aspects

2.4.1. Introduction

GCP

All clinical trials were performed according to the ethical principles of the Declaration of Helsinki and in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirements for the country in which they were conducted.

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.

- Tabular overview of clinical studies

Summary of studies in the Clinical Development for the Meningitis B Vaccine

	Phase	Study Location Year	Age at Enrollment[a,b] (Schedule)	Type of study	Vaccine Group	N enrolled
Early Vaccine Formulation	1	**V72P1** US 2004/05	19-40y (0,1,2,6[c])	single blind randomized controlled	rMenB+OMV (NW) rMenB	15 13
		V72P1E1 US 2005/06	booster 12 months after last vacc. in V72P1	open label extension	rMenB+OMV (NW) rMenB	7 7

	Phase	Study Location Year	Age at Enrollment[a,b] (Schedule)	Type of study	Vaccine Group	N enrolled
		V72P2 US 2004/06	19-40y (0,1,2,6 or 0,2,6[c])	single blind randomized controlled	rMenB+OMV (NW) rMenB Control vaccines (Engerix B for months 0,1,6 and Menomune at month 2)	32 32 14
	2	**V72P3** US 2006/07	11-18y (0,2,6[c])	single blind randomized controlled	rMenB+OMV (NW) rMenB placebo	79 83 41
Final Vaccine Formulation (rMenB+OMV NZ)	1	**V72P5** Switzerland 2006	18-40y (0,1,2[c])	observer blind single center randomized	• rMenB+OMV NZ • rMenB+OMV(NW) • rMenB	28 28 14
	2	**V72P4** Italy, Germany 2007/09	18-50y (0,2,6[c]) (MenACWY at month 7)	open multicenter	• rMenB+OMV NZ	54
		V72P6 UK 2006/08	2 mo (2,4,6,12 or 12 mo)	open multicenter randomized controlled	• rMenB (2,4,6,12) • rMenB+OMV NZ(2,4,6, 12) • rMenB (12) • rMenB+OMV NZ (12)	48 50 25 24
		V72P6E1 2010/going	• booster dose at 40 mo after 4 doses (at 2,4,6,12 mo) • 2 doses at 40,42 mo after one dose at 12 mo • 2 doses at 40,42 mo	Open label single-center extension	• rMenB (2,4,6,12,40) • rMenB+OMV NZ (2,4,6,12,40) • rMenB (12,40,42) • rMenB+OMV NZ (12,40,42) • rMenB+OMV NZ (naive 40, 42)	29 19 14 8 43
		V72P9 UK 2007/08	6-8mo (6,8,12 mo)	Single-blind single-center randomized	• rMenB • rMenB+OMV NZ	30 30
		V72P9E1 2010/12	40, 60 mo • 4th booster dose at 40 mo • 2 doses in naive children (40,42 mo & 60,62 mo)	open label single-center extension	• rMenB (6,8,12,40) • rMenB+OMV NZ (6,8,12,40) • rMenB+OMV NZ (naive 40,42) • rMenB+OMV NZ (naive 60,62)	16 14 41 49
		V72P12[d] Belgium, Italy, Germany, Spain, Czech Republic 2008/10	2mo (2,4,6 or 2,3,4mo)	open multicenter randomized	• rMenB+OMV NZ 2,4,6 or 2,3,4 with concomitant Routine • rMenB+OMV NZ 2,4,6 + Routine (3,5,7) • Routine (2,3,4)	627/318[e] 628 312

	Phase	Study Location Year	Age at Enrollment[a,b] (Schedule)	Type of study	Vaccine Group	N enrolled
		V72P12E1[d] 2009/11	12, 18, 24 mo • 4th booster dose at 12, 18 or 24 mo; • 2 catch up doses at 12-14, 18-20 mo (naive) and in naive children (24-26 mo)	open label multicenter extension	• rMenB+OMV NZ booster at 12, 18 or 24 months of age in subjects who received 3 doses of rMenB+OMV NZ 2,4,6 + Routine at 2,3,4 or 2,4,6 months in V72P12 • rMenB+OMV NZ at 12 and 14 months (in subjects who received routine at 2,3,4) • rMenB+OMV NZ at 18, 20 and at 24, 26 months of age	Total 1588 73+78+106 143+164+174 152+157+188 246 51+56
		V72P16 Czech Republic Hungary Italy Argentina Chile 2009/11	2mo (2,3,4mo)	partially observer-blind multicenter randomized controlled dose-ranging formulation-finding	8 vaccine groups injected with either different composition or formulation process of the meningococcal B antigens (groups I-VI), or with concomitant administration of paracetamol (Par+B+OMV, group VIII), or receiving the control vaccine (MenC, group VII)	Total 1507 949 188 (Group I) 184 (Group VIII) 186
	3	**V72P10**[d] Chile 2008/10	11-17y (1 dose, or 2 doses [0,1 or 0,2], or 3 doses [0,1,2 or 0,2,6 or 0,1,6][c])	observer-blind multicenter randomized controlled	8 vaccine groups injected with different chronologies of rMenB+OMV NZ or placebo at study month 0,1,2,6	Total 1631 375 (1 dose) 628 (2 doses) 628 (3 doses)
		V72P13 Italy, Germany, Austria, Czech Republic, Finland 2008/10	2mo (2,4,6 mo)	partially blinded multicenter randomized controlled	• 3 lots rMenB+OMV NZ with concomitant Routine • Routine • Routine+MenC[f]	2481 (833+828+ 820) 659 490
		V72P13E1 Italy, Germany, Austria, Czech Republic, Finland 2009/10	12mo • 2 catch up doses at 12, 14 or 13, 15 mo • 4th booster dose at 12mo • 1 dose at 12mo	• open label randomized multicenter extension	Each of the three groups from V72P13 were administered a booster MenB at 12 mo and MMRV concomitantly or 1 month afterwards, making 6 groups in total	Total 2249 402 1555 292

	Phase	Study Location Year	Age at Enrollment[a,b] (Schedule)	Type of study	Vaccine Group	N enrolled
		V72P13E2 2010/11	naive 23 mo	open label randomized multicenter extension	• 12 months persistence to 12 months booster given in V72P13E1 • 3rd rMenB+OMV NZ dose to 2-dose catch up subjects of V72P13E1 • 2 rMenB+OMV NZ doses in naive children (24, 26 mo)	Total 508 305 86 116

[a] y – years; [b] mo – months; [c] schedules are in months; [d]V72P12 is phase 2b and its extension V72P12E1; V72P10 and its extension V72P10E1 are phase 2b/3; [e]N=627 for the 2,4,6 rMenB+OMV NZ with concomitant Infanrix Hexa and Prevenar schedule and N= 318 for the 2,3,4 rMenB+OMV NZ with concomitant Infanrix Hexa and Prevenar schedule; [f]Menjugate, Novartis meningococcal C conjugate vaccine; Note: the manufacturing lot numbers for rMenB+OMV NZ used in these studies are detailed in section 5.2

2.4.2. Pharmacokinetics

As per current guidance (CPMP/SWP/465/95), pharmacokinetic studies are not generally required for vaccines; therefore, pharmacokinetic studies (absorption, distribution, metabolism, and excretion) have not been conducted with Bexsero.

2.4.3. Pharmacodynamics

Pharmacodynamic studies were not conducted since, as is common for vaccines, the pharmacodynamic profile for the rMenB+OMV vaccine is defined by its immunogenicity profile.

2.5. Clinical efficacy

No efficacy studies were performed during the clinical development of Bexsero. For practical reasons, meningococcal efficacy trials in non-epidemic settings are not considered feasible. Thus, the licensure application is based on a serological surrogate marker for protection, serum bactericidal antibody (SBA). The SBA measures the level of antibodies that recognize bacterial surface antigens and are capable of directing complement-mediated bacterial lysis, the main mechanism by which *N. meningitidis* serogroup B strains are killed after natural infection.

The primary endpoint of studies contained within this dossier is to determine the proportion of subjects with hSBA titers equal to or above the threshold of 1:4 against each of three reference meningococcal serogroup B strains. The use of this threshold is based on the work by Goldschneider showing that a naturally acquired serum bactericidal antibody titer of ≥1:4 (by SBA using endogenous human complement) provided protection against serogroup C among young adults. In addition efficacy data from the Norwegian OMV vaccine trials suggesting that hSBA titers ≥1:4 correlate with clinical efficacy further supports the use of serum bactericidal antibody as an appropriate surrogate marker for protection against disease caused by meningococcal serogroup B. While in the early studies the percentage of subjects with a titer greater than or equal to 1:4 was calculated, in the phase 2b and 3 studies, the threshold was set to a more conservative 1:5 as this ensures with 95% confidence that

subjects with a titer of 1:5 or greater will have achieved a titer of at least 1:4. This was based on a validation of the Novartis hSBA that has shown that the lower limit of the two-sided 95% confidence interval for a titer of 1:5 is a titer of 1:4, using linear interpolated hSBA titers. In addition to the 1:4 cut-off, data on SBA titers ≥1:8 were provided in some studies, as well as reverse cumulative distribution curves. A higher titre could be correlated to long-term protection.

Selection of Serogroup B Reference Strains

Three reference strains have been selected for the SBA assay. They are virulent strains isolated from cases of invasive disease and each susceptible to killing by serum bactericidal antibodies directed primarily against only one of the three vaccine antigens. The same three reference strains were used in all studies described below. This strategy has been endorsed by the CHMP Scientific Advice procedures. Using human complement as the external complement source in the SBA assay has also been endorsed.

Three validation reports for the serum bactericidal assay have been presented. Using a number of test sera the accuracy, precision, linearity and specificity was determined using a standard design for validation. The method fulfils the appropriately set criteria for the different properties and is therefore suitable for measuring clinical samples for documentation of immunogenicity.

For the fourth vaccine antigen NHBA, no suitable reference SBA strain was available at the time of the clinical development program. A strain was identified late in the clinical program and it has also been validated. At the time of the original application, data was only available from a subset of subjects in study V72P13E1. The Company has submitted additional data from children and adolescents with this strain during the procedure.

Strain	**Vaccine antigen**
NZ98/254	PorA1.4 antigen in the OMV NZ
HH44/76	fHbp
5/99	NadA
M10713*	NHBA

*A suitable reference strain for evaluating NHBA-specific bactericidal killing (strain) was recently been identified (M10713). SBA data are currently available against this strain fromV72P6E1, V72P9E1, V72P10, V72P12E1, V72P13E2, V72P16.

NHBA measurements by ELISA

For the heparin binding protein (NHBA or 287 antigen), no reference strain to measure antigen-specific killing was initially identified. Therefore, ELISA has been used to measure antibody responses against the NHBA/287 antigen throughout clinical development.

The ELISA data from clinical studies demonstrates potent antibody response against the NHBA elicited by the vaccine. More recently, a suitable reference strain, M10713, specifically sensitive to bactericidal antibodies against NHBA was identified to measure SBA in clinical studies in in infants, toddlers, children and adolescents. As the SBA measures functional antibodies killing bacteria, these data are considered more important than ELISA measurements.

Estimation of vaccine coverage

Traditional typing methods such as those based on serological reactivity using reference antibodies (serogrouping, serotyping, serosubtyping) or genetic screening (MLST) are not appropriate means of defining which meningococcal strains will be covered by rMenB+OMV NZ-elicited immune sera.

To assess the potential breadth of coverage of the MenB vaccine against circulating meningococcal strains within a given population, the Applicant has developed a method for assessing whether a given strain is susceptible to killing by antibodies induced against the four major antigen components of the MenB vaccine, PorA, fHbp, NHBA and NadA. The typing method is termed the "Meningococcal Antigen Typing System" or MATS.

In principle the MATS enables far more precise estimation of vaccine coverage than previously possible. As such it represents a significant step forward in the effort to develop broadly protective vaccines against meningococcal disease.

The MATS is not regarded by the Applicant as part of the bioanalytical procedures that needs validation. However, the success of the rMenB+OMV NZ vaccine will depend on the match between antigens in the vaccine and meningococcal strains that cause disease. Therefore, the properties of MATS and the relevance of the relative potency (RP) and positive bactericidal threshold (PBT) should be part of the clinical efficacy evaluation.

To avoid that antibodies specific to other antigens present within the same strain could contribute to the SBA, strains genetically mismatched to the given vaccine antigen were used.

Typing of strains for susceptibility to killing by antibodies directed against the antigens fHbp, NHBA and NadA is performed by means of an ELISA method that measures both the immunological relatedness and the relative level of expression of each vaccine recombinant protein antigen. Finally, the strain panel was tested in hSBA using pooled sera from vaccinees of different age groups, and related bactericidal killing to vaccine antigen phenotype as evaluated by the new assay. From these studies, a model that can be used to estimate the potential effectiveness of a vaccine against diverse strains of MenB was developed.

Overall, the proposed strategy for estimating the efficacy of the rMenB+OMV NZ vaccine is considered acceptable, i.e. first determination of frequency of responders to each antigen, followed by an estimation of proportion of strains susceptible to killing by immune sera. This issue has also been the subject of CHMP Scientific advices.

Novartis has assessed the potential effectiveness of the rMenB+OMV NZ vaccine using a subset of the meningococcal serogroup B strains that are currently available in Europe. This subset, provided by five European reference laboratories, consists of 1053 meningococcal invasive strains isolated during the 2007-2008 epidemiologic year (July 1, 2007 to June 30, 2008) in the following European countries: Norway, UK, Germany, France and Italy. The complete strain panel has now been characterised and based on MATS data derived from the 1052 typeable strains, an estimated 78% (95% CI: 63%; 90%) of strains are predicted to be covered by the vaccine. As MATS does not account for the activity of bactericidal antibodies generated from non-PorA components of OMV or the synergistic effects of the multiple component of Bexsero, this is considered to be a conservative estimate of vaccine strain coverage.

The strain collection covers Western Europe only and epidemiological data from Central and Eastern Europe are still largely lacking, although preliminary reports of strain coverage in the Czech Republic

and Greece were provided during the approval procedure. The Czech and the Greek data were generally in line with the Western European data, 74% (95%CI: 58 – 87%) and 88% (95% CI: 60-96%) respectively, which is reassuring. The Company position that it is important that the epidemiological studies are discussed and planned together with ECDC is endorsed.

The stability of the vaccine antigens has been the subject of a separate study, which included a strain collection from the Netherlands covering 50 years. The results of this study strongly indicate that the presence of vaccine antigen genes is very stable over time.

2.5.1. Dose response studies

No formal dose-response studies were originally performed for this product. The amount of OMV in the vaccine is based on the experience with the OMV vaccine used in New Zealand, which was based on the development of an OMV vaccine in Norway. The doses of the recombinant protein components are based on non-clinical experiments in mice, and generally expected to be in line with other protein vaccines.

The studies included in this section aim to describe choice of OMV component, dosing schedule and to some extent the use of concomitant routine vaccinations.

Composition: The choice of composition was studied in V72P5 for adults, V72P6 for Infants and V72P9 for toddlers (6-8 months). In these studies rMenB with and without OMV was used, and in V72P5 both OMV NZ and OMV NW were included.

Dose schedule: Different dosing schedules in infants were used in study V72P12 (three doses 1-2 months apart), V72P13 (three doses two months apart, immune responses measured after 3rd dose) and V72P6 (three doses two months apart, immune responses measured after 2nd and 3rd dose).

A single booster dose after infant vaccinations was studied in V72P6, V72P13E1 (described in 2.5.2 Main studies) and V72P12E1 after 3 doses. Thus data on booster vaccination after 2 dose priming in infants has not been studied.

Dose schedule in older infants, 6-8 months of age was studied in V72P9, (2+1 doses were given 2 months apart). Unvaccinated toddlers were vaccinated with 2 doses in study V72P13E1 (described in section 2.5.2 Main studies). Unvaccinated children were vaccinated with 2 doses in study V72P13E2, V72P6E1 and V72P9E1 (described in section 2.5.2 Main studies)The dosing schedule was studied in adolescents (11-17 years of age) in V72P10 (described in section 3.4 Main studies). Immune responses after 1, 2 and 3 doses given at least 1 month apart were studied.

The dosing schedule in adults was studied in V72P5 (immune responses measured after 2nd and 3rd dose).

Concomitant vaccinations: The effect of concomitant routine infant vaccinations on rMenB+OMV vaccine was studied in V72P12, and the impact on routine infant vaccinations of concomitant vaccination with rMenB+OMV was studied in V72P12 and V72P13. In study V72P13E1 rMenB+OMV was given with or without concomitant MMR vaccination.

Study V72P5: A Phase 1, Observer Blind, Single-center, Randomized Study of the Safety, Tolerability and Immunogenicity of Novartis Meningococcal B Recombinant Vaccine +/- OMV When Administered at a 0, 1, 2-Month Schedule in Healthy Adults 18-40 Years of Age.

Methodology

This was a Phase I, observer-blind, single-center, randomized study in healthy adults. Novartis Recombinant Meningococcal Vaccine +/- OMV was to be administered intramuscularly (IM) according to a 0-, 1-, and 2-month immunization schedule. A cohort of healthy adults 18 through 40 years of age was to be randomized in a 2:2:1 ratio to one of the following three groups:
Group I - Novartis Meningococcal B Recombinant Vaccine + OMV New Zealand (NZ) at 0, 1, and 2 months: 26 subjects (rMenB + OMV NZ)
Group II - Novartis Meningococcal B Recombinant Vaccine + OMV Norway (NW) at 0, 1, and 2 months: 26 subjects (rMenB + OMV NW)
Group III - Novartis Meningococcal B Recombinant Vaccine without OMV at 0, 1, and 2 months: 13 subjects (rMenB)
Blood samples were collected for meningococcal serology (bactericidal activity and immunoglobulin G [IgG] antibody levels) and selected clinical laboratory tests from all subjects at baseline and during the study (to assess any significant changes from the screening values).

In addition, ad hoc blood samples were collected in a subset of 10 subjects per vaccination group at baseline and at 6 months after the third dose to explore the ability of Novartis Meningococcal B Recombinant Vaccine +/- OMV to elicit long-term B cell memory responses.

Objectives

Immunogenicity Objectives

- To explore the immunogenicity of three dose of Novartis Meningococcal B Recombinant Vaccine +/- OMV in healthy adults at 30 days after the third dose, by evaluation of the breadth of bactericidal activity (SBA) response against a panel of genetically distinct meningococcal strains. Immunogenicity may be explored at other time points.
- To explore the immunogenicity of three doses of Novartis Meningococcal B Recombinant Vaccine +/- OMV in healthy adults at 6 months after the third dose by evaluation of the breadth of SBA response against a panel of genetically distinct meningococcal strains.
- To explore the induction of specific antibody responses by enzyme-linked immunosorbent assay (ELISA) at 30 days after the third dose of Novartis Meningococcal B Recombinant Vaccine +/- OMV. In addition, specific antibody responses by ELISA may be explored at other time points (e.g., at 6 months after the third dose).
- To explore the ability of Novartis Meningococcal B Recombinant Vaccine +/- OMV to elicit long-term B cell memory responses, by in vitro assay evaluation of vaccine specific memory B cell frequency aimed to determine frequencies of circulating memory B lymphocytes that can be induced to release serogroup B meningococcal- (MenB-) or OMV-specific antibodies. Ad hoc blood samples were collected, in a subset of 10 subjects per vaccination group, at baseline and 6 months after the third dose.

Demographic and Other Baseline Characteristics

The average age was 32 years in all three vaccine groups, ranging from 18 to 38 years in the rMenB + OMV NZ group, from 25 to 39 years in the rMenB + OMV NW group, and from 22 to 40 years in the rMenB group. In all three vaccine groups, a majority of the subjects were males (57-86%). Most subjects from all vaccine groups were Caucasian (86-89%). Mean subject weight on enrollment was 70 kg in the rMenB + OMV NZ group, 72 kg in the rMenB + OMV NW group, and 73 kg in the rMenB group. Mean height was 172 cm both in the rMenB + OMV NZ group and in the rMenB + OMV NW group and 175 cm in the rMenB group. The mean body mass index (BMI) was 24 in all three vaccine groups. Study entry criteria were fulfilled by all subjects in all vaccine groups.

Immunogenicity results

Table 1 summarizes the panel of meningococcal B strains used in this study to assess serum bactericidal activity of the investigational vaccines. The criteria for selection of this panel of 15 meningococcal B strains included genetic diversity, clonal complexity, geographic distribution, PorA/B assortment, and year of isolation. This same panel of strains was included in the assessment of the bactericidal activity of these vaccines in the non-clinical immunogenicity studies performed in mice and baboons and the phase 1 clinical studies V72P1 and V72P2. The sequence of the vaccine component protein antigen 287 is derived from N meningitidis strain NZ98/254 (also referred to as 394/98); the sequences for vaccine component antigens 953, 936, and 961c are derived from strain 2996, and the sequence for vaccine component antigen 741 is derived from strain MC58. The OMV vaccine component in rMenB + OMV NZ is derived from strain NZ98/254, while the OMV vaccine component in rMenB + OMV NW is derived from strain HH44/76.

Table 1 Description of the Panel of Genetically Distinct Meningococcal Strains Used in the Study

Strain	Country	Sero Group	Year	ST	ET	Serotyping
5/99	Norway	B	1999	1349	A4	B:2b:P1.5,2
2996	UK	B	1975	540	A4	B:2b:P1.5,2
M6190	USA	B	1999	1988	ET37	B:2a:P1.5,2
GB364	UK	B	2001	11	ET37	B:2a:P1.5,2
95N477	AUS	B	1995	475	ET37	B:2a:P1.2
HH44/76	Norway	B	1976	32	ET5	B:15:P1.7,16:L3,7,9
MC58	UK	B	1985	74	ET5	B:15:P1.17,16b
CU385	Cuba	B	1980	33	ET5	B:4:P1.15
M4105	USA	B	1996	154	Lineage 3	B:4,7:P1.7,4
98/254	New Zealand	B	1998	154	Lineage 3	B:4:P1.4
M1390	USA	B	1995	41	Lineage 3	B:15:B1.7,4
1000	CSI	B	1988	20	other	B:NT:P1.5
M4458	USA	B	1998	new	other	B:NT:P1.3
GB013	UK	B	2001	275	other	B:NT:P1.22,9
M3812	USA	B	1997	60	other	B:NT:P1.5

ST=sequence type, ET=electrophoretic type, AUS=Australia; CSI=Russia; UK=United Kingdom; USA= United States of America

Proportion of Subjects with Bactericidal Titers ≥ 1:4 at One Month After the Third Vaccination

In the rMenB + OMV NZ group and the rMenB + OMV NW group, the proportion of subjects with bactericidal titers ≥ 1:4 increased from baseline to 1 month after the third vaccination for 14 of the 15 tested N meningitidis serogroup B strains (the exception was strain 95N477). In the rMenB group, this was the case for 13 of the strains. For 4 of the strains (HH44/76, 5/99, CU385, and MC58), all subjects in all vaccine groups achieved bactericidal titers ≥ 1:4 at 1 month after the third vaccination. Ninety-three percent of the subjects in the rMenB + OMV NZ group achieved bactericidal titers ≥ 1:4 against strain NZ98/254 at 1 month after the third vaccination, while this percentage was lower in the rMenB + OMV NW group (74%) and in the MenB group (54%). For the other strains, similar percentages of subjects (ranging from 37% to 100%) in the three vaccine groups achieved bactericidal titers ≥ 1:4 at 1 month after the third dose.

Proportion of Subjects with Fourfold Rise in Bactericidal Titer

No major differences were observed between the proportion of subjects with at least 4- fold rise in bactericidal titers at 1 month after the second vaccination and at 1 month after the third vaccination; i.e., the subjects who achieved a 4-fold rise did so after two vaccinations.

The proportion of subjects with at least 4-fold rise in bactericidal titers from baseline was generally somewhat lower than the proportions of subjects with bactericidal titers ≥ 1:4 at the same time point, which might be explained by some subjects having high titers at baseline.

Geometric Mean Bactericidal Titers (GMTs)

For all strains, baseline GMTs were comparable between groups.

Although the titers at 1 month after the third vaccination was the primary immunogenicity variable, GMTs of the same magnitude were observed already at 1 month after the second vaccination.

Enzyme-Linked Immunosorbent Assay (ELISA) Antibody Responses

At 1 month after the third vaccination, geometric mean anti-287-953, anti-936-741, anti-961c, ELISA IgG titres were raised compared to baseline in all three vaccine groups. The ELISA IgG titres against the OMV NW increased after the rMenB+OMV NW and rMenB+OMV NZ vaccinations, but not after the rMenB only vaccination. The two OMV vaccines elicited similar responses to the NW antigen. In contrast, the OMV NZ containing vaccine elicited higher IgG titres against the NZ antigen than the NW OMV-containing vaccine. The rMenB vaccine elicited modest IgG titres against the NZ antigen.

The IgG titres generally increased after a third dose compared to the second dose. Generally the titres had declined at 6 months following the third dose, but remained increased compared to baseline.

Persistence of Immune Responses (Results at Six Months After the Third Vaccination)

When comparing the proportions of subjects with bactericidal titers ≥ 1:4 at 6 months after the third vaccination with those at 1 month after the third vaccination a decrease in the proportion of subjects with bactericidal titers ≥ 4 was observed for a majority of the strains. However, for some strains, unchanged or increased proportions of subjects with bactericidal titers ≥ 1:4 were observed at 6 months after the third vaccination.

Similar trends were observed for the other measures of immunogenicity when comparing the results from 6 months after the third vaccination with the results from 1 month after the third vaccination.

The objective to explore the in vitro assay for evaluation of a vaccine-specific memory B cell induced by Novartis meningococcal B recombinant vaccine +/- OMV was assessed by cell-mediated immunity (CMI). Only a small subset of subjects was identified for the evaluation of the response, which was not expected to give a reliable estimate of B cell maturation.

Ad hoc blood samples were collected in a subset of 10 subjects per vaccination group at baseline and 6 months after the third dose. Memory B cells were measured for antigens 287-953, 936-741 and 961C. The results indicate an increased frequency of B cells after 6 months compared to baseline for antigens 936-741 and 961C, but the sample size is very small, and the variation appears to be large.

Study V72P6: A Phase 2, Open Label, Multi-Center, Controlled, Randomized Study of the Safety, Tolerability and Immunogenicity of Novartis Meningococcal B Recombinant Vaccine±OMV, when Administered to Healthy Infants at 2, 4, 6 and/or 12 Months of Age

Methods

This was a Phase 2, open label, multi-center, controlled, randomized study in healthy infants aged 2 months at time of enrollment. Novartis rMenB Vaccine +/- OMV-NZ was administered intramuscularly (IM) either according to a 2, 4, 6 and 12 months of age immunization schedule, or as a single dose at 12 months of age. After obtaining written informed consent from their parents/legal guardians, eligible healthy infants were randomized in a 2:2:1:1 ratio.

Objectives

Immunogenicity Objective:

Primary

To explore the immunogenicity of Novartis rMenB Vaccine +/- OMV-NZ when administered to healthy infants at 2, 4 and 6 months of age, at 30 days after the third dose, by evaluation of the breadth of bactericidal activity (SBA) response against a panel of genetically distinct meningococcal strains.

A number of secondary objectives relating to SBA responses at various time points were also defined.

Statistical Methods

Due to small sample sizes, the immunogenicity analyses were purely exploratory. No statistical tests were performed. All analyses were analyzed descriptively.

The precision of the immunogenicity point estimates for each vaccine group was expressed by the 95% CI. The adjusted GMTs and GMRs and associated 95% CIs for each vaccine group were to be calculated for each visit and meningococcal strain, by exponentiating (base 10) the least square means of the log-transformed (base 10) titers and their 95% CIs from a two-way analysis of variance (ANOVA) with a factor for vaccine group and center.

Criteria for evaluation

Immunogenicity :

A key immunogenicity parameter of interest is the percentage of subjects with a SBA titer ≥ 1:4 measured at one month after the third immunization. The percentage of subjects with a SBA titer ≥ 1:4 measured at baseline, at one month after the second dose, at 12 months of age and one month later have also been assessed.

Additionally, the percentage of subjects with no detectable bactericidal titers at baseline (SBA <1:4) who had a detectable titer (i.e., SBA ≥1:4) during the study and the associated 95% Clopper-Pearson confidence intervals have been calculated by time point, meningococcal strain and vaccine group.

The percentage of subjects with at least a fourfold rise in titer over the preimmunization titer and the associated 95% CIs have been assessed at 30 days following the second and third injection, at the age of 12 months and at 30 days later by meningococcal strain and vaccine group. The percentage of subjects with at least a fourfold rise in titer at one month after the third injection, at the age of 12 months and 30 days following the fourth (groups I and II) or first (groups III and IV) injection over the pre-third injection and the associated 95% CIs are also assessed by meningococcal strain and vaccine group. In addition, the percentages of subjects with titers greater than or equal to other dilutions besides 1:4 are assessed by meningococcal strain and vaccine group.

The bactericidal titers at each time point and their logarithmic transformation (base 10) and summarization by meningococcal strain and vaccine group was also performed (summarized as GMTs [geometric mean titers] and GMRs [geometric mean ratios]). Measurement of vaccine-specific antibody responses by ELISA or other immune response assays was not performed.

Results

Study population

Overall, 147 infants were enrolled and randomized (2:2:1:1) in this study (Table 11.1-1). Of this total, 79 subjects were included in the Per Protocol (PP) population at one month after second injection and 77 subjects were included in the PP population a month after the third injection. The PP population, a month after booster or first vaccination (for the Routine±OMV groups as they received only one vaccination at 12 months of age) included 112 subjects. The PP population included all subjects in the MITT population without a major protocol deviation.

The demographic and other baseline characteristics were similar across all the four groups, except that more male subjects were enrolled in the Routine±OMV groups.

The mean age was similar in the four vaccine groups at inclusion (60.2 ± 5.3 days; overall mean ±SD). A total of 85 male infants (58%) and 62 female infants (42%) were enrolled. A majority (95%) of the subjects were of Caucasian origin, <1% was of Asian origin, <1% was Black and 4% were of other origin. The mean body weight (4.92 ± 0.79 kg; overall mean ±SD) and height (57.05±3.02 cm; overall mean ±SD) was similar in the four vaccine groups at inclusion. All the randomized subjects met the eligibility criteria.

Immunogenicity results

Immunogenicity of three of the major vaccine antigens in the rMenB±OMV vaccine, as measured by SBA, was determined using the panel of three major meningococcal serogroup B reference strains: strain H44/76-SL, strain 5/99 and strain NZ98/254. The results of the additional strains, UK P1.7-2,4, GB355, GB364 and GB101, and LNP20404 serve to provide supplemental information.

Immunogenicity of three of the major vaccine antigens in the rMenB±OMV vaccine, as measured by SBA, was determined using a panel of three meningococcal serogroup B reference strains.

Four additional meningococcal serogroup B strains (UK P1.7-2, 4, GB355, GB364 and GB101) were used to measure SBA responses following vaccination with Novartis rMenB±OMV Vaccine. These four strains were selected because 1) they are strains which vary in their vaccine antigen composition and/or expression and 2) are representative of the major disease causing types currently in the UK. In addition, serogroup B strain LNP 20404, a clinical isolate from a recent outbreak in Normandy, France was also used to evaluate the SBA response. These strains will be used to investigate the vaccine's ability to induce a cross-reactive SBA response to genetically diverse serogroup B strains.

Results for the Three Major MenB Strains

Proportion of Subjects with Bactericidal titers ≥1:4

As expected, proportion of subjects with bactericidal titers ≥1:4 against NZ98/254 strain was low in the rMenB group [2/37 (5%)]. At 12 months of age (i.e., 6 months after third vaccination), the proportion of subjects with bactericidal titers ≥1:4 declined marginally against H44/76 strain and 5/99 strain. This showed that antibody persisted well against both H44/76 and 5/99 strains. The proportion of subjects with bactericidal titers ≥1:4 remained the same as at a month after third vaccination in the rMenB group against NZ98/254 strain, however in the rMenB+OMV group, there was a decline in titers. At 1 month after the booster injection, an increase in proportion of subjects with bactericidal titers ≥1:4 was observed for all strains except against strain NZ98/254 in the rMenB group.

In comparison, the proportion of subjects with titers ≥1:4 in the Routine+OMV group at baseline, was twice that of the Routine group against strain H44/76, whereas no baseline titers were detected against the other two strains in both groups.

At one month post-vaccination, the proportion of subjects with titers ≥1:4 was highest in the 5/99 strain as expected, and lowest in the NZ98/254 strain in the Routine group versus the Routine+OMV group.

At 12 month of age (pre-booster), the proportion of subjects with titers ≥1:4 in the rMenB group against strains H44/76 and 5/99 were robust and ranged from 70% to 92% and in the rMenB+OMV group ranged from 68% to 88%. In comparison, the proportion of subjects with baseline titers ≥1:4 (12 months) in the Routine group against strains H44/76 and 5/99 ranged from 0% to 9% and in the Routine+OMV group ranged from 0% to 18%. The higher proportion of subjects with robust titers observed in the rMenB±OMV groups, who were vaccinated with three doses in infancy were indicative

of induction of immunological memory and priming by the 3-dose infant series. In comparison, the Routine±OMV groups which received only a single dose at 12 months, proportion of subjects with titers ≥1:4 were very low. The minimal response observed for recipients of the rMenB vaccine without OMV NZ was expected for strain NZ98/254.

Proportion of Subjects with Bactericidal titers ≥1:8

The trends observed in subjects with bactericidal titers ≥1:8 across all three strains were similar to the trends observed in subjects with bactericidal titers ≥1:4, although the percentage of subjects achieving titers ≥1:8 were lower.

Geometric Mean Titers (GMTs), Geometric Mean Ratios (GMRs)

Baseline GMTs were balanced between rMenB and rMenB+OMV groups for all three strains.

At one month after the second vaccination, highest GMT increase was observed against the 5/99 strain in both the rMenB and rMenB+OMV vaccine groups (104 and 71, respectively). Likewise, at one month after the third vaccination, the highest GMT increase was observed against the 5/99 strain in both the rMenB and rMenB+OMV vaccine groups. The lowest was observed against the NZ98/254 strain. The titers against the NZ98/254 strain were much higher in the rMenB+OMV group as expected as compared to the rMenB group. At 12 months (after the 4th dose), the GMT increase was the highest in the 5/99 strain in both the rMenB and rMenB+OMV vaccine groups.

Of the five additional strains baseline titres against one strain, GB101, where quite high, and did not increase substantially after 2 or three doses. No responses were observed against strain GB355, as expected as this strain does not express any of the vaccine antigens. The responses against GB364 were modest, while the responses against UKP1.7-2,4 and LNP20404 were more robust after vaccination with the OMV-containing vaccine.

V72P9: A Phase 2, Single Blind, Single Center, Randomized Study of the Safety, Tolerability and Immunogenicity of Novartis Meningococcal B Recombinant Vaccine ± OMV, when Administered to Healthy Infants 6-8 months old

Methodology:

This was a phase 2, randomized, single blind, single center study in healthy infants aged 6 to 8 months at time of enrollment. The three injections of rMenB Vaccine ± OMV were administered intramuscularly (IM) at enrollment, (6 - 8 months of age), two months later, and at 12 months of age. To obtain at least 48 evaluable subjects, 60 eligible healthy infants 6 to 8 months old at time of enrollment were enrolled after obtaining written informed consent from their parents/legal guardians, to afford for a 20% drop out rate. They were randomized in a 1:1 ratio to one of the following groups:

rMenB: Novartis MenB recombinant vaccine without OMV: 30 subjects

rMenB + OMV: Novartis MenB recombinant vaccine with OMV: 30 subjects Novartis rMenB ± OMV was administered IM into the antero-lateral area of the right thigh.

Immunogenicity Objectives

To explore the immunogenicity of Novartis rMenB Vaccine with or without OMV in healthy infants at 30 days after the second and the third injections by evaluation of the breadth of bactericidal activity (SBA) response against a panel of genetically distinct meningococcal strains.

Statistical methods

The following measures of immunogenicity were assessed:

Bactericidal activity (percentage of subjects with SBA titer ≥1:4 and ≥1:8) against a panel of genetically distinct meningococcal strains prior to the first dose and 30 days following the second and the third dose.

Bactericidal activity was assessed (geometric mean response, geometric mean ratio to baseline, and four-fold rise from baseline) against a panel of genetically distinct meningococcal strains prior to the first dose and 30 days following second and third dose.

Fold rise in titer from baseline and geometric mean concentrations (GMC) of the 287-953 antigen as measured by ELISA at 30 days following the second and third dose.

The immunogenicity analyses were exploratory. However, two-sided statistical tests for differences between the rMenB and rMenB+OMV vaccine groups in their ability to elicit an immune response were to be performed using a categorical linear model, having a factor for vaccine group. No adjustment to account for multiplicity was made.

Sixty subjects were to be enrolled and to receive one of two investigational vaccines, in order to obtain at least 48 evaluable subjects. The sample sizes were selected in order to obtain preliminary safety data and preliminary data regarding the effect of the addition of OMV to rMenB on the humoral immune responses as measured by SBA in healthy infants 6-8 months old.

Results

Demographic and other baseline characteristics

Mean age at first vaccination was similar between the two vaccine groups (7.0, and 7.1 months respectively). Across both vaccination groups, there were 47% and 60% female subjects enrolled as compared to 53% and 40% of male subjects, respectively. The majority of subjects was Caucasian (83%) and balanced between the vaccine groups. The mean height and weight of the subjects were similar between both the vaccine groups. All the randomized subjects met the eligibility criteria.

Immunogenicity results

Summary of Subjects with a SBA Titer ≥ 1:4 and ≥ 1:8 for the Three Major Strains

Proportion of Subjects with Bactericidal titers ≥1:4: One month after the second injection, all subjects in both the vaccine groups achieved bactericidal titers ≥1:4 against the HH44/76 and 5/99 strains. For the NZ98/254 strain, 1 subject (4%) in the rMenB group and 21 subjects (95%) in the rMenB+OMV group achieved bactericidal titers ≥1:4 ($p<0.001$). One month after the third injection, all subjects in both the vaccine groups achieved bactericidal titers ≥1:4 against the H44/76 and 5/99 strains. For the NZ98/254 strain, 2 subjects (9%) in the rMenB group and 23 subjects (96%) in the rMenB+OMV group achieved bactericidal titers ≥1:4 ($p<0.001$). The minimal response observed for recipients of the rMenB vaccine without OMV NZ was expected for strain NZ98/254, as this strain is measuring bactericidal activity primarily against the PorA protein in the OMV NZ component of the vaccine.

Proportion of Subjects with Bactericidal titers ≥1:8: Baseline bactericidal titers ≥1:8 were similar between the vaccine groups among the strains (0 to 4%). One month after the second injection, almost all subjects in both vaccine groups achieved bactericidal titers ≥1:8 against H44/76 and 5/99 strains (range, 96% to 100%). For the NZ98/254 strain, no subject in the rMenB group and 20 (91%) subjects in the rMenB+OMV group achieved bactericidal titers ≥1:8 ($p<0.001$). One month after the third injection, all subjects in both the vaccination groups achieved bactericidal titers ≥1:8 against the

H44/76 and 5/99 strains. For the NZ98/254 strain, bactericidal titers ≥1:8 were achieved by 1 subject (5%) in the rMenB group and 23 subjects (96%) in the rMenB+OMV group and (p<0.001).

Summary of Subjects with a SBA Titer ≥ 1:4 and ≥ 1:8 for the Four Additional Strains

Baseline titers ≥1:8 were not observed in any of the two groups against the UK P1.7-2,4, GB364 and GB355 strains, but were observed in only 2 subjects in the rMenB+OMV group for the GB101 strain.

One month after the second injection, the bactericidal titers of ≥1:8 were achieved against two strains (GB101 and GB364) in the rMenB group and against three strains (UKP1.7- 2,4 , GB101 and GB364) in the rMenB+OMV group. Bactericidal titers of ≥1:8 were achieved by no subjects in the rMenB and 16 (18%) subjects in rMenB+OMV group for the UK P1.7-2,4 strain. For the GB364 strain 14 (74%) rMenB and 11 (69%) rMenB+OMV subjects achieved titers ≥1:8, and for the GB101 strain 2 (9%) rMenB and 7 (33%) rMenB+OMV subjects achieved the same. None of the subjects in either group achieved titers ≥1:8 against the GB355 strain.

One month after the third injection, for the UK P1.7-2,4 strain no subjects in the rMenB, but 21 subjects (95%) in rMenB+OMV group achieved a bactericidal titer ≥1:8 (p<0.001). For GB364 strain, bactericidal titer ≥1:8 was achieved in 12 (71%) rMenB subjects and 16 (84%) rMenB+OMV subjects. For the GB101 strain, 3 (14%) rMenB and 10 (45%) rMenB+OMV subjects achieved the same (p=0.021). None of the subjects achieved the bactericidal titer ≥1:8 at even one month after the third injection for strain GB355.

Enzyme-Linked Immunosorbent Assay (ELISA) Antibody Responses for 287-953 Protein Antigen

Baseline concentrations were similar between the two vaccine groups. At one month after the second and third injections, geometric mean anti-287-953 IgG concentrations were statistically higher in the rMenB+OMV group than the rMenB group.

A significant increase in geometric mean ratios over baseline for the 287-953 protein antigen was observed after the second vaccination (73: rMenB and 139: rMenB+OMV) and a further increase was observed after the third vaccination (100: rMenB and 169: rMenB+OMV) for both vaccine groups.

V72P12: A Phase 2b, Open Label, Randomized, Parallel-Group, Multi-Center Study to Evaluate the Safety, Tolerability and Immunogenicity of Novartis Meningococcal B Recombinant Vaccine When Administered with or without Routine Infant Vaccinations to Healthy Infants According to Different Immunization Schedules.

Methods

This was a Phase 2b, open label, multi-center, randomized, parallel group study in healthy infants aged approximately 2 months at time of enrollment. rMenB+OMV NZ was administered intramuscularly (IM) at 2, 4 and 6, or 2, 3 and 4 months of age.

Subjects were randomized in a 2:2:1:1 ratio per schedule:

- Group 1: One dose of rMenB+OMV NZ at 2, 4, and 6 months of age, administered concomitantly with routine infant vaccinations. (B+R246)
- Group 2: One dose of rMenB+OMV NZ at 2, 4, and 6 months of age; routine infant vaccinations administered at 3, 5 and 7 months of age. (B246+R357)
- Group 3: One dose of rMenB+OMV NZ at 2, 3, 4 months of age, administered concomitantly with routine infant vaccinations. (B234)
- Group 4: Routine infant vaccines administered at 2, 3 and 4 months of age. (R234)

Meningococcal serology was performed at baseline and post-3rd dose of rMenB+OMV NZ for groups 1 - 3 (i.e. groups 1 and 2 at 7 months of age, group 3 at 5 months of age) and post-3rd dose of routine vaccines for group 4 (i.e. 5 months of age). Routine vaccines serology was performed. Blood samples were collected at baseline and post-3rd routine vaccines dose (5 months of age) for those subjects belonging to groups 3 and 4.

Objectives

Immunogenicity:

Primary
1. To demonstrate a sufficient immune response of rMenB+OMV NZ, when given concomitantly with routine infant vaccines to healthy infants at 2, 4 and 6 and 2, 3 and 4 months of age, as measured by percentage of subjects with serum bactericidal activity (SBA) titer ≥1:5, at 1 month after the third vaccination.

Secondary
1. To demonstrate that the immunogenicity of routine infant vaccines, when given concomitantly with rMenB+OMV NZ to healthy infants at 2, 3 and 4 months of age, was non-inferior to that of routine infant vaccines given without rMenB+OMV NZ.
2. To demonstrate that the immunogenicity of rMenB+OMV NZ when given concomitantly with routine infant vaccines was non-inferior to that of rMenB+OMV NZ given without routine infant vaccines at 2, 4 and 6 months of age.
3. To assess the prevalence of meningococcal B antibodies over the study period by evaluation of SBA, at baseline and at 1 month after the third vaccination, in the subjects that received routine infant vaccines without rMenB+OMV NZ.
4. To characterize the immune response against vaccine antigen 287-953, as measured by ELISA, at 1 month after the third vaccination.

Statistical methods

Immunogenicity

For all groups percentages of subjects with hSBA titers ≥1:5 and associated 95% Clopper Pearson CIs were computed at 30 days following three doses for each meningococcal B strain.

The percentage of subjects with antibody response against *B. pertussis*, diphtheria and tetanus toxoid, *H. influenzae* type b, polio, hepatitis B and the 7 pneumococcal antigens a pre-specified level and 95% CI, at one month following the third vaccination were calculated for groups 3 and 4. Differences in these percentages were calculated as well.

The GMCs and 95% CIs were constructed by exponentiating the least squares means of the logarithmically transformed titers and their associated 95% CIs obtained from a two way Analysis of Variance (ANOVA) with factors for vaccine group and study center.

SBA Geometric Mean Titers (GMTs) or ELISA Geometric Mean Concentrations (GMCs) and 95% CIs for the three rMenB+OMV NZ vaccine groups were calculated by exponentiating the least squares means and the lower and upper limits of the 95% CIs of the log transformed titers obtained from a two-way ANOVA with factors for vaccine group and study center.

Results

Disposition of Subjects

A total of 1885 subjects were enrolled and 1799 subjects completed the study. In all, 86 subjects withdrew due to AEs, consent withdrawal, lost to follow-up, inappropriate enrollment, administrative reasons and protocol deviations. No deaths were reported in this study. There were no major differences between the groups.

Demographic and Other Baseline Characteristics

The demographic and other baseline characteristics were balanced across the different vaccination groups. The majority of the immunogenicity subjects were Caucasian (91% to 95%). Gender distributions were similar across the vaccination groups. Age, height and weight were similar across the vaccination groups.

Percentage of Subjects with hSBA Titers ≥1:5

The primary objective was to demonstrate a sufficient immune response of rMenB+OMV NZ, when given concomitantly with routine infant vaccines to healthy infants at 2, 4 and 6 (Group B+R246) and 2, 3 and 4 months of age (Group B+R234), as measured by percentage of subjects with serum bactericidal activity (hSBA) titer ≥1:5, at 1 month after the third vaccination. The results are summarised in Table 2. The results were similar for the PP population.

Table 2 Geometric Mean Bactericidal Titers (GMTs) and Ratios of GMTs (95% CI) - PP Population

		B+R246	B246_R357	B+R234	R234
Strain 44/76-SL		**N=556**	**N=548**	**N=285**	**N=277**
	Baseline	1.49 (1.4-1.59)	1.36 (1.28-1.46)	1.34 (1.23-1.46)	1.28 (1.19-1.37)
	1 Month After 3rd Vaccination	86 (80-92) N=525	113 (105-121) N=534	82 (75-91) N=273	1.16 (1.09-1.24) N=253
	1 Month After 3rd to Baseline	58 (52-64) N=501	83 (74-92) N=507	61 (53-70) N=262	0.91 (0.83-1) N=236
Strain 5/99		**N=551**	**N=537**	**N=280**	**N=275**
	Baseline	1.3 (1.21-1.39)	1.28 (1.2-1.37)	1.19 (1.09-1.3)	1.24 (1.15-1.33)
	1 Month After 3rd Vaccination	537 (494-584) N=527	699 (643-759) N=529	325 (292-362) N=275	1.25 (1.08-1.45) N=236
	1 Month After 3rd to Baseline	430 (379-487) N=497	553 (489-625) N=494	271 (231-318) N=257	1.03 (0.86-1.22) N=217
Strain NZ98/254		**N=554**	**N=543**	**N=283**	**N=278**
	Baseline	1.13 (1.08-1.18)	1.08 (1.04-1.13)	1.06 (1-1.12)	1.07 (1.03-1.1)
	1 Month After 3rd Vaccination	12 (11-14) N=530	18 (16-20) N=534	11 (9.14-12) N=274	1.11 (1.04-1.19) N=257
	1 Month After 3rd to Baseline	11 (9.28-12) N=504	16 (14-19) N=503	10 (8.52-12) N=258	1.05 (0.97-1.14) N=238

A secondary objective was to demonstrate that the immunogenicity of rMenB+OMV NZ when given concomitantly with routine infant vaccines (Group 1 [B+R246]) was non-inferior to that of rMenB+OMV NZ given without routine infant vaccines (Group 2 [B246_R357]) at 2, 4 and 6 months of age (Group 1 vs. Group 2).

Non-inferiority of the immune response for Group 1 (B+R246) compared to Group 2 (B246_R357) was demonstrated for strain H44/76 and for strain 5/99 (2-sided 95% LCLs -1% for both). For strain NZ98/254, however, the 2-sided 95% LCL was -12%; thus, non-inferiority of the immune response to strain NZ98/254 could not be established for Group 1 (B+R246).

After the third rMenB+OMV NZ vaccination, hSBA GMTs against the three strains were similar between Groups 1 (B+R246) and 2 (B+R234). In contrast, a higher increase in hSBA GMTs was seen in the subjects who received the rMenB+OMV NZ vaccination separately from the routine vaccination (Group 2 [B246_R357].

Immune response against vaccine antigen 287-953

The immune response against vaccine antigen 287-953, as measured by ELISA, at 1 month after the third vaccination is summarised in Table 3.

Table 3 Geometric Mean Bactericidal Antibody Concentrations (GMCs) Measured by ELISA against the 287-953 Antigen - PP Population

	B+R246 N=569	B246_R357 N=559	B+R234 N=293	R234 N=287
Baseline	23 (21-24)	23 (22-24)	22 (21-24)	22 (21-23)
1 Month After 3rd Vaccination	3327 (3115-3553) N=545	4244 (3978-4527) N=557	3254 (2988-3545) N=281	21 (20-21) N=269
1 Month After 3rd to Baseline	149 (136-164) N=531	190 (173-208) N=539	145 (128-164) N=275	0.94 (0.89-0.99) N=257

At the baseline the GMCs were similar across the vaccination groups (range 22-23). One month after the third rMenB+OMV NZ vaccination, the GMCs ranged from 3254-4244 with the GMRs being 145-190. GMCs were higher in subjects who received rMenB+OMV NZ separately from the routine vaccines. As expected, there was almost no change in the GMCs in the control Group 4 (R234).

Immunogenicity of routine infant vaccines when given concomitantly with the rMenB+OMV vaccine

The immunogenicity of routine infant vaccines, when given concomitantly with rMenB+OMV NZ to healthy infants at 2, 3 and 4 months of age (Group 3 [B+R234]), was compared to that of routine infant vaccines given without rMenB+OMV NZ (Group 4 [R234]).

For each of the below vaccine components non-inferiority was demonstrated if the lower limit of the two sided 95% confidence interval for the difference in the percentage of subjects with antibody response greater than the pre-specified cut-off for each antigen was greater than -10%.

Diphtheria: Non-inferiority was demonstrated. 100% of the subjects in both groups had antibody levels ≥0.1 IU/mL against diphtheria toxoid. 76% and 84% of the subjects in the rMenB+OMV+ routine and routine only groups respectively had antibody levels ≥1.0 IU/mL against diphtheria toxoid.

Tetanus: Non-inferiority was demonstrated. 100% of the subjects in all groups had antibody levels ≥0.1 IU/mL against tetanus toxoid. 82% and 93% of the subjects in the rMenB+OMV+ routine and routine only groups respectively had antibody levels ≥1.0 IU/mL against tetanus toxoid.

Pertussis: Non-inferiority was demonstrated for seroconversion against FHA, pertactin and PT. In terms of the percentage of subjects achieving a fourfold increase in antibody response, which was an additional secondary analysis, non-inferiority was also demonstrated for all three pertussis antigens.

Polio: Non-inferiority was demonstrated for all three polio types.

Hepatitis B: Non-inferiority was demonstrated. ELISA antibody concentrations ≥10.0 mIU/mL was achieved in 96% of rMenB+OMV+ routine group and in 97% of the routine vaccinated only group.

PRP-Hib: Non-inferiority was demonstrated using the protective cut-off of ≥0.15 µg/mL. In addition, the percentage of subjects with ELISA antibody titres ≥1.0 µg/mL was also calculated, and the lower limit of the 95% CI was -10 using this cut-off.

Pneumococcal: Non-inferiority was demonstrated for the 6 of the7 serotypes included in Prevenar. Non-inferiority for serotype 6B was not demonstrated as the lower limit of the 95% CI was-14%.

Study V72P16 The Company has in response to the Day 120 LoQ submitted an interim report for an ongoing study, V72P16, in which different doses of OMV and recombinant proteins were compared. The final study report shall be submitted (see section 2.7).

In study V72P16 (preliminary report), subjects were vaccinated at 2, 3 and 4 months of age with different formulations of rMenB+OMV NZ with reduced amounts of recombinant proteins and OMV. Bactericidal titers were also found to be lower against strains H44/76 and 5/99 when the recombinant protein components were reduced by one-half (150µg full dose vs. 75µg) while maintaining an unchanged quantity of the OMV component, suggesting that a dose reduction could compromise the protective responses to the fHbp and NadA components of the vaccine.

OMV: The response rate to NZ98/254 decreased from 78% (95% CI: 71; 84) to 67% (95% CI: 59; 74) when the OMV dose was reduced by one-half, and to 56% (95% CI: 48; 64) when a quarter dose was given. The fever (≥38.5°C) rates in the B+OMV and the B+1/2 OMV were very similar (51 and 50% respectively after the first dose). There were no differences in rate of other systemic or local reactions between the full and half dose of OMV together with the full protein dose. Thus, there does not seem to be any advantage of giving half the OMV dose, in terms of improved safety, and the lower immune responses to the OMV component favours the current formulation.

Recombinant proteins: Bactericidal GMTs were lower against strains H44/76 (72 (95% CI: 64; 80) vs. 100 (95% CI; 90M; 112)) and 5/99 (318 (95% CI: 279; 363) vs. 393 (95% CI: 344; 448)) when the recombinant protein components were reduced by one-half (150µg full dose vs. 75µg), suggesting that a dose reduction could compromise the protective responses to the fHbp and NadA components of the vaccine. The SBA responses to the NHBA component were unexpectedly low in this study, and no responses to different protein doses were presented.

In conclusion, the proposed dose of OMV, fHbp and NadA are considered justified, although there is limited data on the NHBA component.

2.5.2. Main studies

Pivotal clinical studies

The pivotal studies include two main study populations, i.e. infants from 2 months of age (study V72P13) and 12 to 15 months of age (study V72P13E1), and children and adolescents 11-17 years of age (V72P10 in Chile). The infant program used a 3+1 dose schedule administered during the first year of life. A two-dose catch-up program during the second year of life was used in study V72P13E1. In adolescents different schedules from one to three doses given one to two months apart was used in study V72P10.

Infants study

V72P13: A Phase 3, Partially Blinded, Randomized, Multi-Center, Controlled Study to Evaluate Immunogenicity, Safety and Lot to Lot Consistency of Novartis Meningococcal B Recombinant Vaccine When Administered with Routine Infant Vaccinations to Healthy Infants

Booster/catch-up_study:

V72P13E1: A Phase 3, Open label, Multi-Center, Extension Study to Evaluate the Safety, Tolerability and Immunogenicity of Novartis Meningococcal B Recombinant Vaccine When Administered as a Booster at 12 Months of Age or as a Two-dose Catch-up to Healthy Toddlers Who Participated in Study V72P13

Adolescent study:

V72P10: A Phase 2b/3, Multi-Center, Observer-Blind, Controlled Study of the Safety, Tolerability and Immunogenicity of Novartis Meningococcal B Recombinant Vaccine Administered to Healthy Adolescents Aged 11-17 Years According to Different Vaccination Schedules

Methods

Study Participants

Infant study:

The study population comprised healthy 2-month old infants (55-89 days, inclusive), who were born after full term pregnancy with an estimated gestational age ≥37 weeks and a birth weight ≥2.5 kg; for whom a parent/legal guardian had given written informed consent after the nature of the study had been explained, and who were available for all the visits scheduled in the study. If required by local regulations, both parents gave written informed consent. Subjects who had previously received a Men B, DTaP-IPV-HBV-Hib, or pneumococcal antigen-containing vaccine, or who had previous ascertained or suspected disease caused by *N meningitidis*, or who had household contact with or intimate exposure to an individual with laboratory-confirmed *N meningitidis*, were excluded.

Booster/catch-up study

The study population consisted of healthy 12-month-old toddlers (0/ +59 days) who completed study V72P13; for whom parent(s)/legal guardian had given written informed consent after the nature of the study was explained. Subjects were recruited from the same sites as in V72P13 in Europe.

Adolescent study:

Main Criteria for Inclusion and Exclusion: Individuals eligible to be enrolled into this study were male and female subjects who were 11 to 17 years of age, who gave written informed consent, who were available for all the scheduled visits and were in good health as determined by the outcome of medical history, physical examination and clinical judgment of the investigator.

Treatments

Infant study: Subjects meeting the enrolment criteria were assigned to one of five vaccination groups (ratio 4:4:4:3:3). The rMenB lot1 group, the rMenB lot2 group and the rMenB lot3 group received one dose of rMenB+OMV NZ (Lot 1, or Lot 2, or Lot 3, respectively) at 2, 4, and 6 months of age concomitantly with the routinely administered infant vaccines (Infanrix Hexa and Prevenar). The Routine group received only the routinely administered infant vaccines at 2, 4, and 6 months of age. The MenC+Routine group received the routinely administered infant vaccines plus Menjugate at 2, 4 and 6 months of age.

Table 4 Time and Events – Overall

N Subjects Groups	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
	2-Months	**4-Months**	**6-Months**	**7-Months**	**12-Months**
800 rMenB lot1 **800 rMenB lot2** **800 rMenB lot1**	Blood draw* **rMenB+OMV NZ** Routine Vaccination	**rMenB+OMV NZ** Routine Vaccination	**rMenB+OMV NZ** Routine Vaccination	Blood draw*	Safety Follow-up
600 Routine	Blood draw Routine Vaccination	Routine Vaccination	Routine Vaccination	Blood draw	Safety Follow-up
600 MenC+Routine	**Menjugate** Routine Vaccination	**Menjugate** Routine Vaccination	**Menjugate** Routine Vaccination		Safety Follow-up

* for subjects in the immunogenicity subset

Booster/catch-up study

Subjects were assigned to receive a booster or catch-up vaccinations or a single dose of rMenB+OMV NZ according to whether they received the primary rMenB+OMV NZ and routine vaccination or routine vaccination only in V72P13. All subjects received one dose of combined Measles, Mumps, Rubella and Varicella vaccine (MMRV) at 12 or 13 months of age. Other vaccines could be given during the course of the trial as long as all Inclusion and no Exclusion Criteria were met. These vaccines should not be administered concomitantly with rMenB+OMV NZ and they were not part of study evaluations.

- **Group 1:** Subjects who received rMenB+OMV NZ and routine vaccination in the parent trial were randomly allocated to Group 1a or Group 1b in a 1:1 ratio:
    - Group 1a [12B12M (1a)] received a booster dose of rMenB+OMV NZ at 12 months of age concomitantly with one dose of MMRV.
    - Group 1b [12B13M (1b)] received a booster dose of rMenB+OMV NZ at 12 months. One dose of MMRV was given at 13 months of age.
- **Group 2**: Subjects who received routine vaccination only in the parent trial were randomly allocated to Group 2a or Group 2b in a 3:1 ratio:
    - Group 2a [12M13B15B] received MMRV at 12 months of age and two catch-up doses of rMenB+OMV NZ at 13 and 15 months of age.
    - Group 2b [12M12B14B] received two catch-up doses of rMenB+OMV NZ at 12 and 14 months of age. One dose of MMRV was given concomitantly at 12 months of age.

Adolescent study

Approximately 1625 subjects were planned to be randomized in an observer-blind manner into one of 8 groups in 1:2:1:2:1:2:3:1 ratio stratified by age group into 11 to 13 years and 14 to 17 years. For the primary vaccination period (visit-1 to visit-4) these groups have been combined into 5 groups as given in Table 3; the groups that were combined differed in their schedules only after visit-4. The number of subjects to be enrolled into each of the vaccine groups, vaccination and blood draw schedules are given in Table 5.

Table 5 Overview of Vaccine Groups Up to Visit-4

Vaccine Groups	Visit-1	Visit-2	Visit-3	Visit-4
	Month 0	**Month 1**	**Month 2**	**Month 3**
Groups 1a & 1b (rMenB0) N=375	Blood draw **rMenB+OMV NZ**	Blood draw Placebo	Blood draw Placebo	Blood draw
Groups 2a & 2b (rMenB01) N=375	Blood draw **rMenB+OMV NZ**	Blood draw **rMenB+OMV NZ**	Blood draw Placebo	Blood draw
Groups 3a & 3b (rMenB02) N=375	Blood draw **rMenB+OMV NZ**	Blood draw Placebo	Blood draw **rMenB+OMV NZ**	Blood draw
Group 4 (rMenB012) N=375	Blood draw **rMenB+OMV NZ**	Blood draw **rMenB+OMV NZ**	Blood draw **rMenB+OMV NZ**	Blood draw
Group 5 (Placebo) N=125	Blood draw Placebo	Blood draw Placebo	Blood draw Placebo	Blood draw

The vaccine groups have been analyzed until one month after the third vaccination (visit-4) as per the schedule given in Table 5. An additional dose was administered at month 6.

Objectives

Infant study:

Immunogenicity, Primary:

- To show the consistency of immune response from 3 lots of rMenB+OMV NZ, by serum bactericidal activity geometric mean titer response (hSBA GMTs), when administered to healthy infants at 2, 4 and 6 months of age, at 1 month after the third vaccination.
- To assess the immunogenicity of 3 doses of rMenB+OMV NZ (3 lots combined) given to healthy infants at 2, 4 and 6 months of age concomitantly with routine infant vaccines, by evaluation of the serum bactericidal activity (hSBA), at 1 month after the third vaccination.

Immunogenicity, Secondary:

- To assess the consistency of immune response from 3 lots of rMenB+OMV NZ, as measured by percentage of subjects with hSBA titer ≥ 1:5 when administered to healthy infants at 2, 4 and 6 months of age, at 1 month after the third vaccination.

- To demonstrate that the immunogenicity of routine infant vaccines when given concomitantly with rMenB+OMV NZ at 2, 4 and 6 months of age, is non-inferior to that of routine infant vaccines given without rMenB+OMV NZ.
- To assess the prevalence of meningococcal B antibodies over the study period by evaluation of the serum bactericidal activity (hSBA), at baseline and at 1 month after the third vaccination, in the subjects that received routine infant vaccines without rMenB+OMV NZ.
- To characterize the immune response against vaccine antigen 287-953, as measured by ELISA, at 1 month after the third vaccination.

Booster/catch-up study

Immunogenicity:

Primary

Demonstration of a sufficient immune response following a fourth (booster) dose of rMenB+OMV NZ administered at 12 months of age, either with or without concomitant MMRV vaccination, to toddlers previously primed with three doses of rMenB+OMV NZ as infants in Study V72P13. The immune response was assessed by the percentage of subjects with serum bactericidal assay (SBA1) titers ≥1:5 at one month after the fourth dose, directed against N. meningitidis serogroup B reference strains H44/76, NZ98/254 and 5/99. The primary criterion to determine a sufficient immune response was that for the percentage of subjects with SBA titers ≥1:5 the lower limit of the two- sided 95% CI was ≥75% for all three reference strains.

Secondary

- Demonstration that the immune responses to MMRV vaccination, when administered concomitantly with the fourth (booster) dose of rMenB+OMV NZ at 12 months of age, are not inferior to the immune responses of MMRV when given alone.
- Assessment of the immune response following a fourth (booster) dose of rMenB+OMV NZ administered at 12 months of age, either with or without concomitant MMRV vaccination, as measured by SBA GMTs and percentage of subjects with SBA titers ≥1:5 at one month after the fourth dose of rMenB+OMV NZ, directed against N. meningitidis serogroup B reference strains H44/76, NZ98/254 and 5/99.
- Evaluation of the persistence of bactericidal antibodies at 12 months of age (predose 4) in infants who previously received three doses of rMenB+OMV NZ as infants in Study V72P13, as measured by SBA GMTs and the percentage of subjects with SBA titers ≥1:5, directed against N. meningitidis serogroup B reference strains H44/76, NZ98/254 and 5/99.
- Demonstration of the induction of immunological memory in infants who previously received three doses of rMenB+OMV NZ as infants in Study V72P13, by comparing the SBA GMT response in toddlers administered the fourth dose of rMenB+OMV NZ at 12 months of age to the response in naïve toddlers receiving a single dose of rMenB+OMV NZ at 12 months of age.
- Evaluation of the immunogenicity of a two-dose catch-up schedule of rMenB+OMV NZ given at 13 and 15 months or 12 and 14 months to naïve toddlers, as measured by SBA GMTs and percentage of subjects with SBA titres ≥1:5 one month after the second dose.
- Characterization of the immune response against vaccine antigen 287-953, as measured by ELISA, one month after the fourth (booster) dose given at 12 months of age, or one month after the first dose and one month after the second meningitidis serogroup B reference strains H44/76, NZ98/254 and 5/99. Antibody responses to rMenB+OMV NZ vaccine antigen 287-953

and MMRV antigens were measured by ELISA. SBA against additional serogroup B strains may be performed to further characterize the immune response to rMenB+OMV NZ vaccination.

Adolescent study:

Primary

- To assess the immunogenicity, safety and tolerability of one, two (0,1 or 0,2 schedule) or three doses (0, 1, 2 schedule) of Novartis rMenB+OMV NZ in healthy adolescents, by evaluation of the serum bactericidal activity using human complement (SBA) response at one month after the last rMenB+OMV NZ dose.

Secondary

- To assess the immunogenicity, safety and tolerability of an additional dose of Novartis rMenB+OMV NZ given at Month 6, by evaluation of the serum bactericidal activity using human complement (SBA) response at one month after the month 6 rMenB+OMV NZ dose, for schedules 0; 0,1 and 0,2.
- To assess the antibody persistence following various vaccination schedules of one, two (0, 1 or 0, 2 schedule) or three doses (0, 1, 2 schedule) of Novartis rMenB+OMV NZ.

Outcomes/endpoints

In the clinical studies of rMenB+OMV NZ, the human complement SBA assay has been performed at two locations: the clinical serology laboratories at Novartis Vaccines, Marburg, Germany (V72P13, V72P13E1), and the Health Protection Agency laboratories in Manchester, England (V72P10). The early (Phase 1 and 2) studies were performed by evaluating the percentages of subjects achieving hSBA ≥1:4 (regarded as protective) and 1:8 as outcomes. In later studies, the lower cut-off was changed from 1:4 to 1:5. Using the 1:5 cut-off ensures with 95% confidence that subjects with hSBA of 1:5 or greater will have achieved a titer of at least 1:4, which is the titer regarded as protective. This was based on a validation of the Novartis hSBA assay that has shown that the lower limit of the two-sided 95% confidence interval for a titer of 1:5 is a titer of 1:4, using linearly interpolated hSBA titers. It should be noted, however, that hSBAs performed outside the Novartis Marburg laboratory (in this application, study V72P10), the ≥1:4 cut-off continued to be used.

Infant study:

Primary

- Immunogenicity of the 3 lots of rMenB+OMV NZ were considered equivalent if, for each of the 3 strains and each pair of vaccine lots, the two-sided 95% CI on the ratio of GMTs at 1 month after the third vaccination was contained within the interval [0.50, 2.00].
- Bactericidal activity (percentage of subjects with hSBA titer ≥1:5) 30 days following the third vaccination (receiving either rMenB+OMV NZ (Lot 1, Lot 2 and Lot 3) .The immune response for the Norwegian strain H44/76, New Zealand strain NZ98/254 and 5/99 strain were sufficient if the lower limit of the 95% CI for the % ≥1:5 for the three lots combined is ≥70%.

- The success criteria for this study were composite, based on the two co-primary objectives. The first objective was to demonstrate that the hSBA response of the three commercial lots were equivalent following the third dose of rMenB+OMV NZ. Once this objective was achieved, the data from the three lots were combined and the sufficiency of the overall hSBA response post-third dose with rMenB+OMV NZ was to be demonstrated. Novartis considered this study a success if, for each of the serogroup B reference strains and for each pair of vaccine lots, the two-sided 95% CI of the ratio of hSBA GMTs at one month following the third vaccination was contained within the interval [0.5, 2.00]; and for each of the serogroup B reference strains, the lower limit of the 95% CI for the percentage of subjects with hSBA titers % ≥1:5 at one month post-dose 3 was ≥ 70%.

Secondary

Immunogenicity of the 3 lots of rMenB+OMV NZ was considered equivalent if, for each of the 3 strains and each pair of vaccine lots, the two-sided 95% CI on the difference of percentage of subjects with hSBA titer ≥1:5 at 1 month after the third vaccination was contained within the interval [-10%, 10%].

The prevalence of meningococcal B antibodies over the study period was assessed by evaluation of the serum bactericidal activity (hSBA), at baseline and at 1 month after the third vaccination, in the subjects that received routine infant vaccines without rMenB+OMV NZ.

Characterization of immune response against vaccine antigen 287-953, as measured by ELISA, one month after the third dose, at 7 months of age.

For routine vaccines, the following analyses were performed:

The immune response one month after third vaccination with B. pertussis, diphtheria and tetanus toxoid, *H. influenzae* type b, hepatitis B and the 7 pneumococcal antigens was measured by ELISA. The percentage of subjects with antibody response against the antigens above a pre-specified level, at one month following the third vaccination, was determined in accordance with Table 2-4 below. The immune response to Polio type 1, type 2, and type 3 vaccine was measured by neutralization test (NT).

Immunogenicity of the routine infant vaccines, when given concomitantly with rMenB+OMV NZ at 2, 4 and 6 months of age, was considered non-inferior to that of routine infant vaccines given alone, for any of the antigens, if the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with antibody response greater than or equal to the cut-off level for that antigen {$P_{\text{Concomitant Vaccine +rMenB+OMV NZ}}$ minus $P_{\text{Concomitant Vaccine}}$} was greater than -10%.

Geometric mean concentrations (GMCs) were also calculated for the antigens of the concomitant vaccines. For the pertussis component, the immunogenicity of InfanrixHexa given concomitantly with rMenB+OMV NZ was considered non-inferior to that of InfanrixHexa alone if the ratio of GMCs (GMC rMenB+OMV NZ+InfanrixHexa / GMC InfanrixHexa) was ≥0.67 after vaccination at 2, 4, and 6 months of age.

Booster / catch-up study

Immunogenicity Criteria:

Primary: The primary criterion to determine a sufficient immune response was that for the percentage of subjects with SBA titers ≥1:5 the lower limit of the two-sided 95% CI was ≥75% for each of the three serogroup B reference strains.

Secondary

- Immunogenicity of MMRV, when given concomitantly with a fourth dose of rMenB+OMV NZ at 12 months of age, was considered non-inferior to that of MMRV given alone, for any of the antigens of MMRV, if the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with antibody response {PMMRV + rMenB+OMV NZ minus PMMRV} was greater than -10%.
- The immune response of the fourth (booster) dose of rMenB+OMV NZ, when administered with or without MMRV at 12 months of age (Groups 12B12M (1a) and 12B13M (1b)), was analyzed descriptively by SBA GMTs, ratios of GMTs, percentage of subjects with SBA titers ≥1:5 and difference in percentages of subjects with SBA titers ≥1:5.
- The persistence of antibodies was evaluated descriptively by SBA GMTs and percentage of subjects with SBA titer ≥1:5 in 12-month-old toddlers.
- The immune response after a two-dose catch-up series in toddlers was evaluated descriptively by SBA GMTs and percentage of subjects with SBA titers ≥1:5.
- Induction of immunological memory following three doses of rMenB+OMV NZ at 2, 4 and 6 months of age was to be demonstrated by showing a booster response following a fourth dose of rMenB+OMV NZ at 12 months of age. A booster response was demonstrated if the lower limit of the two-sided 95% CI for the ratio of the SBA GMTs following a fourth dose of rMenB+OMV NZ at 12 months of age compared to the SBA GMTs following a single dose of rMenB+OMV NZ at 12 months of age (GMT Post-dose 4 / GMT Post-dose 1) was ≥2.0.

Adolescent study

Primary: The percentage of subjects with an hSBA titer ≥1:4 measured at baseline, Month-1, Month-2, Month-3 were calculated. For each meningococcal B strain for which hSBA was measured, the percentage of subjects with a titer ≥1:4 and the associated 95% Clopper-Pearson confidence intervals (CIs) were tabulated.

Secondary: The percentage of subjects with a hSBA titer ≥1:8 measured at baseline, Month 1, Month 2, Month 3 were calculated. For each meningococcal B strain for which hSBA is measured, the percentage of subjects with a titer ≥1:8 and the associated 95% Clopper- Pearson CIs were tabulated. The percentage of subjects with at least a fourfold rise in hSBA titer over the prevaccination titer and the associated 95% Clopper-Pearson CIs were calculated by meningococcal B strain at month-1, month-2 and month-3.
Adjusted geometric mean titers (GMTs), geometric mean ratios (GMRs), and their associated 95% CIs were computed for each visit and meningococcal B strain by exponentiating (base 10) the least square means of the log-transformed (base 10) titres and their 95% confidence intervals from a two-way analysis of variance (ANOVA) with factors for vaccine group and center.For Placebo group, unadjusted geometric mean titres (GMTs) and 95% CIs were computed.
Additionally, all the above-mentioned criteria were also analyzed stratified by prevaccination titer (i.e. hSBA titer <1:4 and ≥1:4). Titers below the limit of detection were set to half the limit of detection for the purpose of analysis. Additionally, median, minimal, and maximal titers were calculated.

Sample size

Infant study:

The assumptions for sample size calculations were based on the within group variance observed for each strain in the Novartis V72P6 infants study post-3rd dose. With 350 evaluable subjects per lot

assayed for strains H44/76, 5/99 and NZ98/254, the power to reject the null hypothesis associated with the primary lot-to-lot immunogenicity objective and demonstrate immunologic consistency for each strain is >99%, >99%, 98% for H44/76, 5/99, and NZ98/254, respectively for an underlying highest to lowest GMT ratio of 1.0. Assuming the results for the three strains are independent, the overall power to demonstrate immunologic consistency is equal to 98%.

Based on the antibody response of infants in Novartis study V72P6 who received 3 doses of the rMenB+OMV NZ (N=40 to 43) vaccine at 2, 4 and 6 months of age, the percentage of subjects with a hSBA titer ≥ 1:4 at 1 month after the third vaccination was 88% (H44/76), 86% (NZ98/254), 95% (5/99) (non-interpolated hSBA results). The primary criterion for a sufficient immune response is that the lower limit of the two-sided 95% CI for the percentage of subjects with a hSBA titer ≥ 1:5 at 1 month following the third vaccination is ≥ 70% for strains H44/76, NZ98/254 and 5/99 for the three lots combined. The power of this co-primary endpoint is 97% assuming 180 evaluable subjects and 85%, 85% and 93% of the subjects showing hSBA titer ≥ 1:5 after three doses of rMenB OMV NZ for each of the three strains. Assuming 1050 evaluable subjects the power is >99%.

Booster/catch-up study:

The assumptions for sample size calculations were based on antibody response of infants in study V72P6 The primary criterion for immunogenicity following the fourth dose of rMenB+OMV NZ was that the lower limit of the two-sided 95% CI for the percentage of subjects with a SBA titer ≥1:5 at one month following the fourth vaccination was ≥75% for all three strains. Therefore, if the true percentage of subjects with bactericidal titers ≥1:5 was 90% for a strain following fourth vaccination of rMenB+OMV NZ and there were 120 evaluable subjects for immunogenicity testing, then the probability (e.g., or power) that the lower limit of the two-sided 95% confidence interval for the true percentage would be 75% or greater was 99%. Therefore, the power was 97% for at least 120 subjects, and 3 reference strains.

The overall power for the primary objective, (a sufficient immune response should be demonstrated for rMenB+OMV NZ administered with and without MMRV) was 94% (97% x 97%).

Adolescent study:

The assumptions for sample size calculations were based on antibody response of adults in study V72P5 study. As a fourth strain still had to be identified, calculations were made for three strains with expected responses of 95% and 85%. The primary criterion for immunogenicity was that the lower limit of the twosided95% CI for the percentage of subjects with an hSBA titer ≥1:4 at 1 month following the first, second or third rMenB+OMV NZ vaccination was ≥85% for strains with an expected response of 95%, and is ≥75% for a strain with an expected response of 85%. Therefore, as described above, if the true percentage of subjects with bactericidal titres ≥1:4 is 85% for a strain following the first, second or third vaccination of rMenB+OMV NZ and there are 300 evaluable subjects for immunogenicity testing, then the probability (e.g., or power) that the lower limit of the two-sided 95% confidence interval for the true percentage will be 75% or greater (e.g., see 1st percentile row under column heading of 85% and N = 300) is 99%.

Randomisation

Infant study

Healthy infants in Europe (Italy, Germany, Austria, Finland and Czech Republic), meeting the enrolment criteria were assigned to one of five vaccination groups (ratio 4:4:4:3:3).

1200 subjects were planned to be enrolled in Finland, Italy, Germany, Switzerland and Austria in an observer-blind way (i.e. each subject's parents or caretakers, as well as the investigators evaluating the subject would be blinded as to whether the subject received rMenB+OMV NZ or Menjugate).

Subjects for the open label immunogenicity subset were enrolled in the Czech Republic and Finland (approx. 2400 subjects planned). They were randomized in a 1:1:1:1 ratio to the rMenB lot1 group, the rMenB lot2 group, the rMenB lot3 group, or the Routine only group.

Subjects who met the study admission criteria were enrolled in to the study and were assigned a 6-digit subject number. The first two digits identified the study site. The next four digits identified the subject within the site and were assigned sequentially, with 0001 corresponding to the first subject enrolled.

Booster/catch-up study

Subjects who met the study admission criteria were enrolled into the study and retained the same unique 6 digit subject number assigned to them for the original V72P13 study. The extension of the open-label part (immunogenicity part) of the parent trial V72P13 was conducted in Czech Republic and Finland (maximum approximately 2600 subjects), as in V72P13. Subjects who received rMenB+OMV NZ + routine vaccination in the parent trial were randomized into Group 12B12M (1a) or 12B13M (1b) in a 1:1 ratio in the extension trial. Subjects who received routine vaccination only in V72P13 were randomized into Group 12M13B15B or 12M12B14B in a 3:1 ratio. The first subjects randomized to each subgroup (in all sites in Finland, and in selected sites in Czech Republic) were asked to give blood samples at the designated time points. The extension of the observer-blind part (safety part) of the parent trial V72P13 was conducted in all countries, which participated in the observer-blind part (safety part) in V72P13 (maximum approximately 1000 subjects).

Adolescent study:

Subjects were randomly assigned in a 1:2:1:2:1:2:3:1 ratio to one of the vaccination groups, following a randomization list created by the Biostatistics and Clinical Data Management (BCDM) department, Novartis Vaccines. Two randomization lists, one for each age group were provided to each Investigator and were used only by the unblinded study personnel to assign the subjects to the vaccination groups.

Blinding (masking)

Infant study: The trial was designed as partially open label, and partially observer-blind.

Open-label part of the study
Both the study personnel and the subject's parent/guardian knew which vaccine was being administered.

The reason for the open label approach in some countries was to provide information about the specific impact of rMenB+OMV NZ on the safety (albeit randomized, open-label) and immunogenicity profile of Infanrix Hexa and Prevenar and separate this impact from the confounding contribution of Menjugate in the randomized, observer blind component of the study. In conclusion the blinded part of the trial minimizes bias in the assessment of safety, whereas the open label part of the trial adds to the safety information whilst ensuring an unbiased assessment of immunogenicity.

Observer-blind part of the study
During the study, designated nurse(s) or physician(s) were responsible for administering the study vaccines to the subjects, and were instructed not to reveal the identity of the study vaccines neither to the subject's parent/guardian nor to the investigative site personnel (investigator, study nurse) involved in the monitoring or conduct of the trial, except in an emergency. This (these) designated

individual(s) had no contact with the subjects after the administration of the study vaccine. If the study vaccine code was supplied to the investigator in the event of an emergency, the Novartis Regional Clinical Research Associate (CRA) or delegate was to be notified immediately by the investigator. The date and time, along with the reason for the unblinding, was to be noted. Study vaccine codes were not to be freely available to the investigator or personnel monitoring the trial until after the completion of the trial and the final data review.

Booster/catch-up study

The study was conducted as an open-label trial. As such, the investigator and his/her study personnel as well as the subject's family knew which vaccine was being administered.

The investigator or his delegate administered the vaccine as indicated on the randomization list. Adherence to the randomization was verified by the Novartis Regional Clinical Research Associate (CRA) or delegate by checking the vaccination records maintained in the investigator's study file.

Note: Subjects randomized to the blinded part of the parent V72P13 study were to remain blinded in the extension study as to whether they received 3 doses of rMenB+OMV NZ or of Menjugate in the first year of life (i.e. remain blinded for their treatment assignment in V72P13), until the database for V72P13 was unblinded.

Adolescent study:

Because the presentation of the two study vaccines were different, the trial was designed as an observer-blind study. During the study, designated nurse(s) or physician(s) were responsible for administering the study vaccines to the subjects. The subjects and the investigative site personnel (investigator, study nurse) involved in the monitoring or conduct of the trial, were unaware of the vaccine identity, except in an emergency.

Statistical methods

For all three studies the main population was the Per Protocol population (PP). Immunogenicity analyses were possibly to be performed on both PP and modified ITT (MITT) population. For the Infant and Toddler studies percentages of subjects with hSBA titres ≥1:5 and associated 95% Clopper Pearson CIs were computed for each strain. In the Infant study antibody response was sufficient if for each of the strains the lower limit of the 95% CI for the % ≥1:5 for the three lots combined (groups I+II+III) was ≥70%. In the Toddler study the antibody response was sufficient if for each strain the lower limit of the two-sided 95% CI for the percentage of subjects with SBA titer ≥1:5 one month after the fourth dose was ≥75%.

In the Adolescent study the percentage of subjects with hSBA titer ≥1:4 and ≥1:8, the point estimates along with the associated 95% Clopper-Pearson confidence intervals (CIs) were to be tabulated. The purpose of stratification by age group (into 11 to 13 and 14 to 17 years) for the randomization was to ensure a thoroughly representative sample of subjects aged 11 to 17 years and no analysis was to be done stratified by age group.

Consistency in the Infant study: For the three rMenB+OMV NZ lots, GMTs and 95% CIs were calculated by exponentiating (base 10) the least squares means and the lower and upper limits of the 95% CIs of the log transformed titers (base10) obtained from a two-way Analysis of Variance (ANOVA) with factors for vaccine lot and study center. Additionally, rMenB+OMV NZ lot-to-lot GMT ratios were computed for each pair of rMenB+OMV NZ lots. Ninety five percent CIs for the ratios of GMTs were constructed by exponentiating the difference of the least square means of the log-transformed titers and the lower and upper limits of the 95% CIs on the difference obtained from the ANOVA model

above. The three rMenB+OMV NZ vaccine lots were considered equivalent if for each of the 3 strains and each pair of vaccine lots, the two-sided 95% CI on the ratio of GMTs at 1 month after the third vaccination was contained within the interval [0.50, 2.00].

The ANOVA was the primary statistical methodology. As a sensitivity analysis to incorporate possible baseline imbalance among the lots, an analysis of covariance (ANCOVA) was also run, incorporating log10 pre-vaccination titers as a covariate along with vaccine lot and center as factors in the model.

Results

Participant flow

Figure 1 Infant study: Subjects analysed flowchart

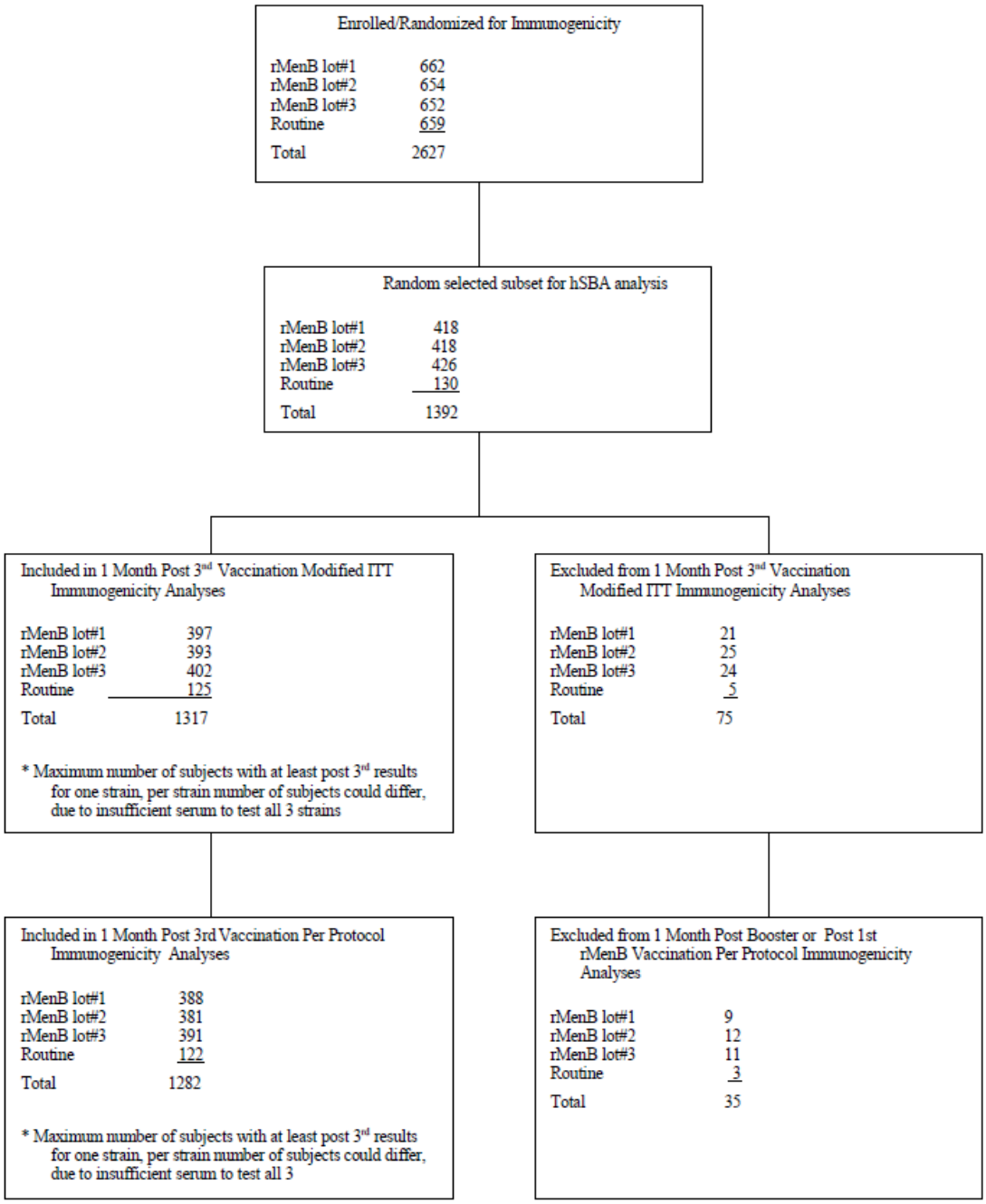


Figure 2 Booster / catch-up study

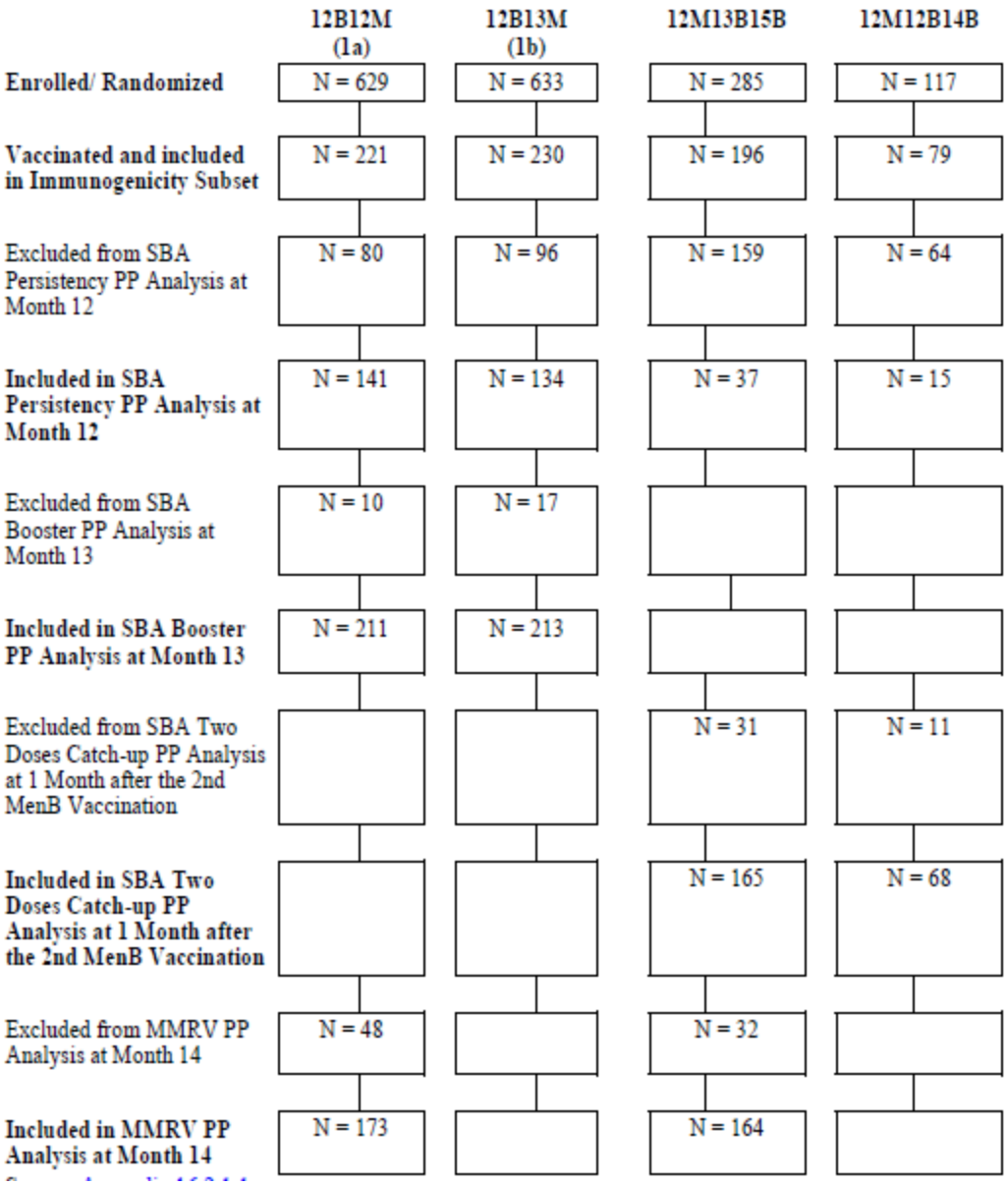
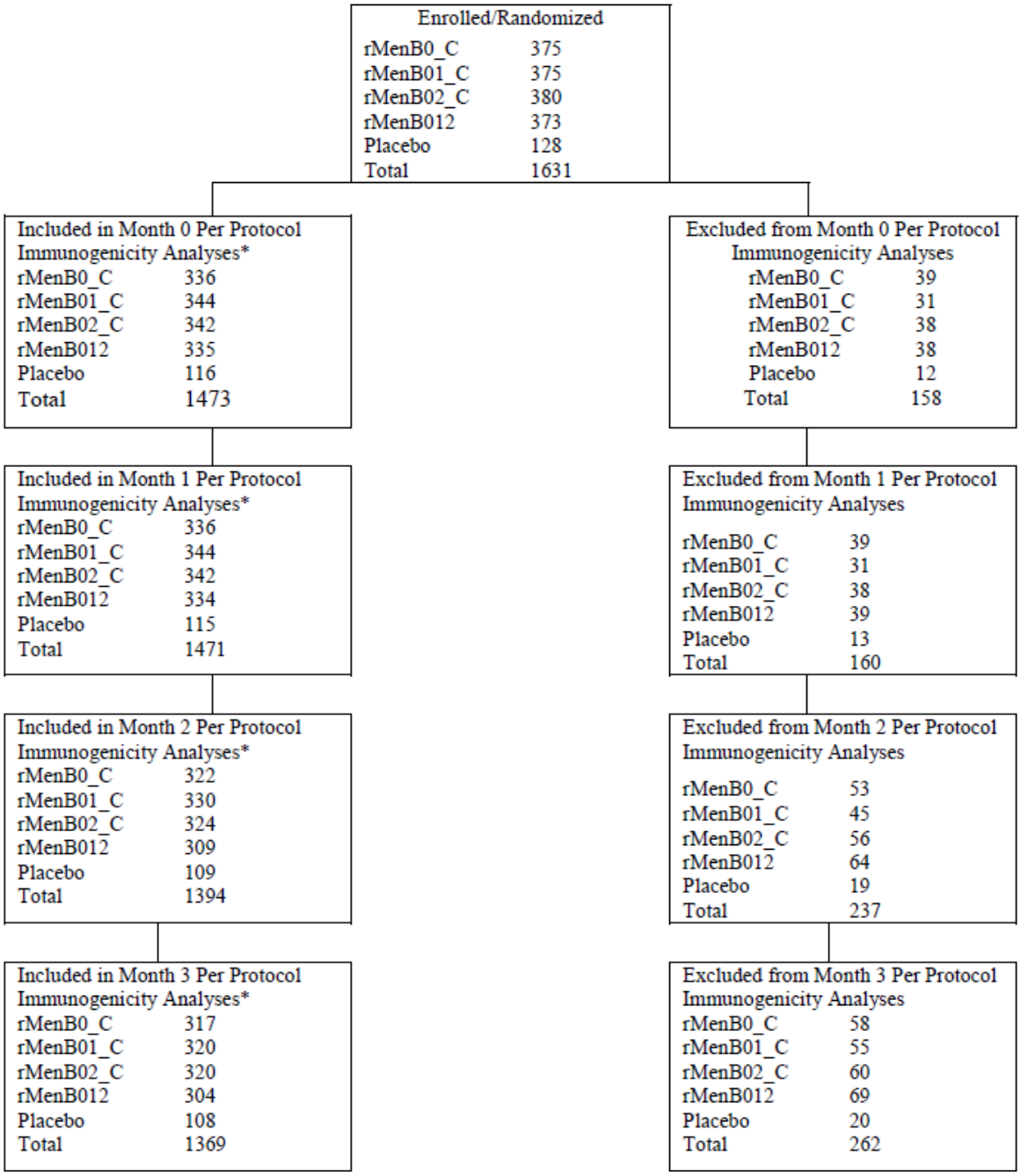


Figure 3 - **Adolescent study**:_Subject completion flow chart



Baseline data

Infant study

The demographic and other baseline characteristics were balanced across the different vaccination groups (Table 6). The majority of the immunogenicity subjects were Caucasian (99% to 100%). Gender distributions were similar across the vaccination groups. Age, height and weight were similar across the vaccination groups.

Table 6 Demography and Baseline Characteristics – Immunogenicity Per Protocol Population

	rMenB lot1 N=388	rMenB lot2 N=381	rMenB lot3 N=391	Routine N=122	Total N=1282
Age (days, mean ±95% CI)	74.3±9.2	75.0±8.9	74.2±9.0	72.5±9.2	74.3±9.1
Sex:					
Male	210(54%)	200(52%)	193(49%)	65(53%)	668(52%)
Female	178(46%)	181(48%)	198(51%)	57(47%)	614(48%)
Ethnic Origin:					
Asian	0	1(<1%)	0	0	1(<1%)
Caucasian	384(99%)	380(100%)	390(100%)	121(99%)	1275(99%)
Other	4(1%)	0	1(<1%)	1(<1%)	6(<1%)
Weight (kg, mean ±95% CI)	5.76±0.72	5.77±0.71	5.72±0.73	5.72±0.76	5.75±0.72
Height (cm, mean ±95% CI)	59.53±2.31	59.48±2.48	59.53±2.44 (N=390)	59.54±2.52 (N=121)	59.51±2.42 (N=1280)
Birth Weight (kg, mean ±95% CI)	3.52±0.43	3.51±0.45	3.49±0.45	3.55±0.45	3.51±0.44
Duration of Pregnancy (weeks, ±95% CI)	39.6±1.2	39.6±1.2	39.5±1.2	39.7±1.2	39.5±1.2

Booster / catch-up study:

The demographic and other baseline characteristics were balanced across the different vaccination groups. Age, sex ratios, height and weight were similar across the vaccination groups.

Table 7 Demography and Other Baseline Characteristics – Enrolled Population

	12B12M (1a) N=629	12B13M (1b) N=633	12M13B15B N=285	12M12B14B N=117	12B12M (3a) N=137	12B13M (3b) N=156	12B12M_C N=152	12B13M_C N=140	Total N=2249
Age (Months):	12.3±0.5	12.3±0.5	12.3±0.5	12.3±0.5	12.2±0.5	12.2±0.4	12.2±0.5	12.2±0.4	12.3±0.5
Sex:									
Male	339 (54%)	303 (48%)	154 (54%)	62 (53%)	62 (45%)	75 (48%)	90 (59%)	67 (48%)	1152 (51%)
Female	290 (46%)	330 (52%)	131 (46%)	55 (47%)	75 (55%)	81 (52%)	62 (41%)	73 (52%)	1097 (49%)
Weight (kg):	10.03±1.13 (N=627)	10.04±1.25	9.98±1.19 (N=284)	10.06±1.18	9.93±1.16 (N=136)	9.92±1.06 (N=154)	10.10±1.16 (N=151)	9.88±1.13 (N=139)	10.01±1.18 (N=2241)
Height (cm):	76.75±2.89 (N=625)	76.86±3.18 (N=628)	76.73±2.94 (N=284)	76.85±3.01 (N=116)	75.71±3.79 (N=136)	76.11±2.89 (N=153)	75.90±3.28 (N=151)	75.51±3.08 (N=139)	76.54±3.11 (N=2232)
Met Protocol Criteria:									
Yes	624 (99%)	622 (98%)	279 (98%)	114 (97%)	132 (96%)	151 (97%)	149 (98%)	137 (98%)	2208 (98%)
No	5 (<1%)	11 (2%)	6 (2%)	3 (3%)	5 (4%)	5 (3%)	3 (2%)	3 (2%)	41 (2%)

Adolescent study:

The demographic and baseline characteristics were similar in all the vaccination groups. The demographic features of the per protocol population were similar to that of the enrolled population.

Table 8 Demographic and Other Baseline Characteristics in Subjects Aged 11 to 17 Years - Enrolled Population

	rMenB0	rMenB01	rMenB02	rMenB012	Placebo
	N=375	N=375	N=380	N=373	N=128
Age (Years±SD):	13.8±1.9	13.9±1.9	13.7±1.9	13.8±1.9	13.8±2.0
Sex:					
Male	152 (41%)	162 (43%)	169 (44%)	174 (47%)	62 (48%)
Female	223 (59%)	213 (57%)	211 (56%)	199 (53%)	66 (52%)
Ethnic Origin:					
Asian	0	0	0	1(<1%)	0
Hispanic	370 (99%)	375 (100%)	376 (99%)	370 (99%)	128 (100%)
Other	5 (1%)	0	4 (1%)	2 (<1%)	0
Weight (kg±SD):	54.76±11.30	56.39±13.17	56.14±11.70	57.76±13.95	56.24±13.18
Height (cm±SD):	157.7±9.2	157.6±9.7	158.0±9.4	158.4±9.9	158.4±9.8
Met Protocol Criteria:	[a]374 (100%)	375 (100%)	380 (100%)	[a]372 (100%)	128 (100%)

a Percentage of subjects was rounded off- even if all subjects did not meet the protocol entry criteria, the percentage is 100%

Summary of Main immunogenicity Results

Infant study

Lot-to-Lot Consistency

Lot-to-lot consistency of the immune response to the rMenB+OMV NZ vaccine given concomitantly with routine infant vaccines is demonstrated in Table 9. Immunogenicity of the 3 lots of rMenB+OMV NZ would be considered equivalent if, for each of the 3 strains and each pair of vaccine lots, the two-sided 95% CI on the ratio of GMTs at 1 month after the third vaccination was contained within the interval [0.50, 2.00]. These criteria were met for all strains.

Table 9 Geometric Mean hSBA Titers and Ratios of Titers (95% CI), and Lot-to-Lot Ratios of Titers, by Meningococcal Strain

Strain		rMenB lot1	rMenB lot2	rMenB lot3	rMenB lot1 : rMenB lot2	rMenB lot1 : rMenB lot3	rMenB lot2 : rMenB lot3
44/76		**N=384**	**N=379**	**N=394**			
	Baseline	1.21 (1.14-1.29) N=383	1.19 (1.12-1.27)	1.19 (1.12-1.27)	1.01 (0.94-1.09)	1.01 (0.94-1.09)	1 (0.93-1.07)
	1 Month After 3rd Vaccination	87 (80-95)	98 (90-106) N=377	85 (78-93) N=388	0.9 (0.81-0.99)	1.02 (0.93-1.13)	1.14 (1.03-1.27)
	1 Month After 3rd Vaccination to Baseline	75 (68-83) N=369	85 (76-94) N=356	73 (66-81) N=373	0.88 (0.77-1.02)	1.02 (0.89-1.18)	1.16 (1.01-1.33)
5/99		**N=385**	**N=380**	**N=390**			
	Baseline	1.21 (1.14-1.3)	1.2 (1.12-1.28) N=379	1.21 (1.13-1.29)	1.01 (0.93-1.1)	1.01 (0.92-1.1)	0.99 (0.91-1.08)
	1 Month After 3rd vaccination	598 (550-651) N=384	681 (626-741)	607 (558-661) N=388	0.88 (0.78-0.98)	0.99 (0.88-1.1)	1.12 (1-1.26)
	1 Month After 3rd vaccination to Baseline	493 (439-552) N=370	568 (506-637) N=359	506 (451-568) N=369	0.87 (0.74-1.01)	0.97 (0.84-1.13)	1.12 (0.96-1.31)
NZ98 /254		**N=386**	**N=380**	**N=394**			
	Baseline	1.03 (1-1.06)	1.06 (1.03-1.1)	1.04 (1-1.07)	0.97 (0.93-1.01)	0.99 (0.95-1.04)	1.03 (0.98-1.07)
	1 Month After 3rd Vaccination	15 (13-17) N=385	14 (12-16) N=378	15 (14-17) N=389	1.04 (0.88-1.23)	0.96 (0.81-1.13)	0.92 (0.78-1.08)
	1 Month After 3rd Vaccination to Baseline	14 (13-17) N=369	13 (12-15) N=357	15 (13-17) N=376	1.08 (0.9-1.29)	0.97 (0.81-1.16)	0.9 (0.75-1.08)

The second co-primary objective of the study was to assess immunogenicity of the rMenB+OMV NZ vaccine given concomitantly with routine infant vaccinations, by evaluating the percentages of subjects achieving hSBA titers of 1:5 or above at one month after the third vaccination. This analysis was performed on the pooled subjects receiving the 3 lots of rMenB+OMV NZ once lot-to-lot consistency had been demonstrated. To meet the second co-primary objective, the lower limit of the 2-sided 95% confidence interval should be ≥ 70% for strains H44/76, 5/99 and 98/254. This criterion was met for all 3 strains. Percentages of subjects achieving hSBA titers ≥1:5 at one month after the third rMenB vaccination are given in Table 10.

Percentages of subjects achieving hSBA titers ≥1:8 at one month after the third rMenB vaccination ranged from 72% against strain NZ98/254 to 100% against the other two strains. A similar pattern is seen for the percentages of subjects achieving at least fourfold increase in titer one month after the

third vaccination, ranging from 71% against strain NZ98/254 to 99% against strain H44/76 and 100% against strain 5/99.

Table 10 Percentage (95% CI) of Subjects with hSBA Titers ≥1:5

Strain		rMenB All	Routine
44/76-SL		**N=1156**	**N=119**
	Baseline	35 (3%) (2-4)	4 (3%) (1-8)
	1 Month After 3rd Vaccination	1146 (100%) (99-100) N=1149	3 (3%) (1-7) N=117
5/99		**N=1154**	**N=120**
	Baseline	45 (4%) (3-5)	8 (7%) (3-13)
	1 Month After 3rd Vaccination	1149 (100%) (99-100) N=1152	2 (2%) (0-6) N=116
NZ98/254		**N=1160**	**N=121**
	Baseline	14 (1%) (1-2)	1 (1%) (0.021-5) N=120
	1 Month After 3rd Vaccination	965 (84%) (82-86) N=1152	2 (2%) (0-6)

Another secondary objective was to characterize the immune response against vaccine antigen 287-953, as measured by ELISA, at 1 month after the third vaccination. At this time point, ELISA GMCs in subjects receiving rMenB+OMV NZ increased 156-fold compared to baseline values (Table 11). In contrast, in subjects receiving routine vaccines, post-third dose GMC changed very little from baseline.

Table 11 ELISA Geometric Mean Concentrations (GMCs) against the 287-953 Antigen

	rMenB lot1 N=615	rMenB lot2 N=600	rMenB lot3 N=611	rMenB All N=1823	Routine N=113
Baseline	22 (21-23) N=611	22 (21-22) N=596	22 (21-23)	22 (21-22) N=1818	21 (20-21)
1 Month After 3rd Vaccination	3149 (2960-3352)	3484 (3270-3712)	3103 (2915-3304) N=608	3370 (3270-3472)	22 (21-23)
1 Month After 3rd Vaccination to Baseline	147 (135-159) N=590	163 (150-177) N=572	141 (130-153) N=592	156 (150-162) N=1754	1.06 (0.99-1.14) N=109

Immunogenicity of routine infant vaccines when given concomitantly with the rMenB+OMV vaccine

For each of the below vaccine components non-inferiority was demonstrated if the lower limit of the two sided 95% confidence interval for the difference in the percentage of subjects with antibody response greater than the pre-specified cut-off for each antigen was greater than -10%.

Diphtheria: Non-inferiority was demonstrated. 100% of the subjects in all groups had antibody levels ≥0.1 IU/mL against diphtheria toxoid. 80% and 86% of the subjects in the rMenB+OMV and routine groups respectively had antibody levels ≥1.0 IU/mL against diphtheria toxoid.

Tetanus: Non-inferiority was demonstrated. 100% of the subjects in all groups had antibody levels ≥0.1 IU/mL against tetanus toxoid. 91% and 95% of the subjects in the rMenB+OMV and routine groups respectively had antibody levels ≥1.0 IU/mL against tetanus toxoid.

Pertussis: Non-inferiority was demonstrated for seroconversion against FHA, pertactin and PT. In terms of the percentage of subjects achieving a fourfold increase in antibody response, which was an additional secondary analysis, non-inferiority was demonstrated for the pertussis FHA and PT antigens. The lower limit of the interval for the pertactin component was -16% and so non-inferiority could not be shown based on this analysis.

Polio: Non-inferiority was demonstrated for polio types 1 and 3. The lower limit of the interval for the polio type 2 component, however, was -11% and so non-inferiority was not demonstrated.

Hepatitis B: Non-inferiority was demonstrated. ELISA antibody concentrations ≥10.0 mIU/mL was achieved in 98% of rMenB+OMV+ routine group and in 100% of the routine vaccinated only group.

PRP-Hib: Non-inferiority was demonstrated using the protective cut-off of ≥0.15 µg/mL. In addition, the percentage of subjects with ELISA antibody titres ≥1.0 µg/mL was also calculated, and the lower limit of the 95% CI was >-10 also using this cut-off.

Pneumococcal: Non-inferiority was demonstrated for the 7 components of Prevenar.

Booster/catch-up study

The primary objective was the demonstration of a sufficient immune response following a fourth (booster) dose of rMenB+OMV NZ administered at 12 months of age, either with (12B12M (1a)) or without (12B13M (1b)) concomitant MMRV vaccination, to toddlers previously primed with three doses of rMenB+OMV NZ as infants in Study V72P13. Overall, the immune response in terms of distribution of SBA titers achieved by subjects was very similar between the 12B12M (1a) and 12B13M (1b) groups for each of the reference strains (Table 12).

Table 12 Number (%) of Subjects with SBA Titers ≥1:5 at 1 Month After Booster Vaccination - PP Population

	Strain H44/76		Strain 5/99		Strain NZ98/254	
	12B12M (1a) N=211	12B13M (1b) N=215	12B12M (1a) N=210	12B13M (1b) N=213	12B12M (1a) N=211	12B13M (1b) N=215
Baseline[a]	171 (81%) (75-86)	177 (82%) (77-87)	206 (98%) (95-99)	212 (100%) (97-100)	41 (19%) (14-25)	52 (24%) (19-30)
1 Month After Booster	210 (100%) (98-100) N=210	212 (100%) (98-100) N=212	209 (100%) (98-100) N=209	212 (100%) (98-100) N=212	204 (97%) (93-99)	200 (94%) (90-97) N=213

The SBA GMTs at 1 month after the booster vaccination are summarised in Table 13. For all three strains the increase in SBA titers was similar in subjects with or without concomitant MMRV vaccination.

Table 13 SBA Titers of Subjects at 1 Month After Booster Vaccination – PP Population

	Strain H44/76		Strain 5/99		Strain NZ98/254	
	12B12M (1a) N=211	12B13M (1b) N=215	12B12M (1a) N=210	12B13M (1b) N=213	12B12M (1a) N=211	12B13M (1b) N=215
Baseline	11 (9.27-12)	10 (9.11-12)	81 (71-93)	81 (71-92)	2.07 (1.8-2.38)	2.21 (1.92-2.55)
1 Month After Booster	139 (123-156) N = 210	119 (105-133) N = 212	1503 (1339-1686) N = 209	1429 (1274-1603) N = 212	39 (33-46)	32 (27-37) N = 213
1 Month After Booster/Baseline	13 (12-14) N = 207	11 (10-13) N = 209	18 (16-21) N = 205	18 (16-20) N = 207	19 (16-22) N = 208	15 (12-17) N = 210

Immune response against vaccine antigen 287-953

The immune response against vaccine antigen 287-953, as measured by ELISA, one month after the fourth (booster) dose given at 12 months of age (groups 12B12M (1a), 12B13M (1b) and Men246 (combined groups 1a and 1b)), or one month after the first dose and one month after the second dose of a two-dose catch-up regimens (12M13B15B and 12M12B14B) at 12 months of age are summarised below.

Table 14 Immune response against vaccine antigen 287-953, as measured by ELISA GMC, one month after the fourth (booster) dose given at 12 months of age - PP Population

	12B12M (1a) N=213	12B13M (1b) N=216	Men246 N=428
Baseline	390 (351-433) N=212	389 (349-434)	390 (361-420)
1 Month After Booster	6225 (5571-6956)	5608 (5111-6154) N=214	5908 (5496-6350) N=427
1 Month After Booster to Baseline	16 (14-18) N=211	14 (13-16) N=212	15 (14-16) N=423

Persistence of antibodies

The persistence of antibodies up to 6 months after primary vaccination is summarised in Table 15. Subjects in 12B12M (1a) and 12B13M (1b) received rMenB+OMV NZ vaccination concomitantly with routine infant vaccines at 2, 4 and 6 months of age in the parent study V72P13. Group Men246 represents subjects from groups 12B12M (1a) and 12B13M (1b) combined. As a control for SBA persistence, these subjects were compared to subjects in Group Routine246 who only received the routine infant vaccines at 2, 4 and 6 months of age in V72P13. Group Routine246 was comprised of subjects from groups 12M13B15B and 12M12B14B in this study combined.

Just before the booster vaccination (at 12 months of age), the SBA titers decreased for all three strains. The decrease in SBA titers was similar across the vaccination groups.

At 12 months of age, the SBA titers were still higher than the respective titers at baseline in V72P13 study and were also higher than the 12-month titers in Routine 246 group who did not receive the rMenB+OMV NZ vaccination in V72P13 study for strains HH44/76 and 5/99. For strain NZ98/254 at12 months the SBA titers had decreased to almost the level of respective titers at baseline in V72P13 study, but were still higher than the 12-month titers in Routine 246 group.

Table 15 Evaluation of Antibody Persistence as Measured by SBA GMTs in 12-Month-Old Previously Primed Toddlers - PP Population

		12B12M (1a)	12B13M (1b)	Men246	Routine246
Strain H44/76		N=139	N=133	N=272	N=51
	1 Month After 3rd Vac. in P13	91 (81-104)	83 (73-94)	87 (79-95)	1.19 (1.07-1.33)
	Pre-Booster Vac. in P13E1	11 (9-12)	10 (8.7-12)	10 (9.28-12)	1.08 (0.99-1.17)
	Pre-Booster Vac. in P13E1 to 1 Month After 3rd Vac. in P13	0.12 (0.1-0.13)	0.12 (0.11-0.14)	0.12 (0.11-0.13)	0.91 (0.81-1.02)
Strain 5/99		N=139	N=133	N=272	N=51
	1 Month After 3rd Vac. in P13	615 (538-704)	620 (540-712)	617 (560-680)	1 (1-1)
	Pre-Booster Vac. in P13E1	85 (72-100)	79 (67-94)	82 (73-92)	1.03 (0.97-1.09)
	Pre-Booster Vac. in P13E1 to 1 Month After 3rd Vac. in P13	0.14 (0.12-0.16)	0.13 (0.11-0.15)	0.13 (0.12-0.15)	1.03 (0.97-1.09)
Strain NZ98/254		N=139	N=132	N=271	N=52
	1 Month After 3rd Vac. in P13	12 (10-15)	14 (12-17)	13 (11-15)	1.07 (0.94-1.21)
	Pre-Booster Vac. in P13E1	2.04 (1.72-2.43)	2.02 (1.69-2.42)	2.03 (1.79-2.3)	1 (1-1)
	Pre-Booster Vac. in P13E1 to 1 Month After 3rd Vac. in P13	0.17 (0.14-0.2)	0.14 (0.12-0.17)	0.15 (0.14-0.18)	0.94 (0.82-1.07)

Induction of immunological memory

The fourth secondary objective was demonstration of the induction of immunological memory in 12 month old children who previously received three doses of rMenB+OMV NZ, by comparing the SBA GMT response after the fourth dose of rMenB+OMV NZ at 12 months of age (12B12M (1a)) to the response in naïve 12-month old children receiving a single dose of rMenB+OMV NZ at 12 months of age (12M12B14B). Immunological memory and a booster response was demonstrated if the lower limit of the two-sided 95% CI for the ratio of the SBA GMTs following a fourth dose of rMenB+OMV NZ at 12 months of age compared to the SBA GMTs following a single dose of rMenB+OMV NZ at 12 months of age was ≥ 2.0.

For all three strains the immune responses to a single booster dose at 12 months of age were higher than the responses to a first dose in 12 month old naïve children (Table 16). Thus, the criteria for demonstrating the presence of immunological memory were met for all three strains.

Table 16 SBA GMTs in Children Administered the Fourth Dose of rMenB+OMV NZ Vs SBA GMTs in Children Receiving a Single Dose of rMenB+OMV NZ At 12 Months of Age (Induction of Immunological Memory) – PP Population

	Strain H44/76			Strain 5/99			Strain NZ98/254		
	12B12M (1a) N=211	12M12B14B N=71	12B12M (1a) : 12M12B14B	12B12M (1a) N=210	12M12B14B N=72	12B12M (1a) : 12M12B14B	12B12M (1a) N=211	12M12B14B N=72	12B12M (1a) : 12M12B14B
Baseline	11 (9.32-12)	1.18 (0.96-1.46)	8.88 (7.04-11)	83 (73-93)	1 (0.81-1.24) N=71	80 (65-99)	2.05 (1.83-2.31)	1.03 (0.84-1.26) N=71	2.02 (1.6-2.54)
1 Month After Booster or 1st rMenB	140 (123-159) N=210	15 (12-19)	8.84 (7.06-11)	1538 (1337-1769) N=209	58 (46-74)	25 (20-31)	39 (34-46)	4.18 (3.18-5.5)	9.36 (7.06-12)
1 Month After Booster or 1st rMenB to Baseline	13 (12-15) N=207	13 (10-16) N=70		19 (16-21) N=205	59 (47-74) N=71		19 (16-22) N=208	3.98 (3.06-5.19) N=71	

Immunogenicity of a two-dose catch-up schedule

The results of a two-dose catch-up schedule of rMenB+OMV NZ given at 13 and 15 months of age (12M13B15B) or 12 and 14 months of age (12M12B14B) to naïve children, as measured by SBA GMTs after the second dose are summarised in Table 17. The increase in SBA titers was similar in both 13 and 15 months (12M13B15B) or 12 and 14 months (12M12B14B) dose catch-up schedules for all three strains.

All subjects in both groups had SBA titers ≥1:5 one month after the second catch-up dose against all three strains, except for strain NZ98/254 in the 12+14-month group (96% responded).

Table 17 SBA Titers One Month after a Two-Dose (Given at 13 and 15 Months or 12 and 14 Months) Catch-Up Schedule of rMenB+OMV NZ in Unprimed Children - PP Population

	Strain H44/76		Strain 5/99		Strain NZ98/254	
	12M13B15B	12M12B14B	12M13B15B	12M12B14B	12M13B15B	12M12B14B
	N=163	N=67	N=164	N=67	N=164	N=68
Baseline	1.24 (1.15-1.35) N=161	1.22 (1.07-1.38)	1.06 (1-1.13) N=160	1.03 (0.94-1.13)	1.03 (0.98-1.07) N=162	1.03 (0.97-1.1) N=67
1 Month After 2nd Vac.	271 (237-310)	248 (201-306)	599 (520-690)	627 (502-783)	43 (38-49)	32 (26-40)
1 Month After 2nd Vac. to Baseline	217 (185-255) N=159	203 (158-261) N=66	560 (478-656) N=159	620 (485-793) N=66	43 (37-49) N=161	31 (25-38) N=67

SBA to strain M10713 after the fourth (booster) dose

At the time study V72P13E1 was initiated, a suitable MenB reference strain to measure bactericidal activity directed against the 287 antigen itself was not available. As such, ELISA was used as an alternative to evaluate the immunogenicity of the 287-953 fusion antigen following vaccination with rMenB+OMV NZ. Since the completion of this study, an acceptable reference strain for measuring SBA to the 287 antigen was identified (strain M10713). As a result, a subset of 100 subjects from groups 12B12M (1a) and 12B13M (1b) was selected and evaluated for SBA responses against strain M10713 one month after the fourth (booster) dose of rMenB+OMV NZ administered at 12 months of age.

Pre-booster dose at 12 months, the percentage of subjects with SBA titers ≥ 1:5 against strain M10713 was 61% for the subjects in groups 12B12M (1a) and 12B13M (1b) combined (group Men246). One month after the fourth (booster) dose of rMenB+OMV NZ, the percentage of subjects achieving the bactericidal titer ≥5 increased to 98%, while 96% of the subjects achieved the 1:8 titer or greater. GMTs against M10713 increased from a pre-booster GMT of 7.99 to a post-booster GMT of 42 (GMR 5.28), demonstrating a robust bactericidal booster response to strain M10713.

Immune Response to MMRV Vaccination

The first secondary objective was to demonstrate that the immune responses to MMRV vaccination, when administered concomitantly with the fourth (booster) dose of rMenB+OMV NZ at 12 months of age (12B12M (1a)), were not inferior to the immune responses to MMRV when given alone (12M13B15B).

The immunogenicity in group 12B12M (1a) was considered non-inferior to that in group 12M13B15B, if for any of the antigens, the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with antibody response greater than or equal to the specified cut-off level for that antigen was greater than -10%. This analysis was performed for the subjects with negative baseline concentrations.

The non-inferiority criterion was achieved for the vaccine antigens Measles, Mumps and Rubella at the specified cut-off levels of ≥255 mIU/mL, ≥10 U/mL and ≥10 IU/mL, respectively. For Varicella, the non-inferiority was demonstrated for the cut-off level of ≥1.25 gp ELISA units/mL (seroconversion) but could not be demonstrated for the higher cut-off level of ≥5 gp ELISA units/mL (seroprotection). The immune response was measured after the first dose of the licensed 2 dose series for the MMRV vaccine used in the study (Priorix-Tetra).

Adolescent study:

Study V72P10 was conducted in Chile, and the relevance to a European population has been discussed. The levels of pre-existing antibodies to fHbp, NadA and PorA were similar among the Chilean adolescents and European adults. No data on expression of vaccine antigens on circulating MenB strains in Chile are available. As no data on adolescents are available from Europe, it is not possible to compare the same age groups from different regions. The applicant will provide data on EU adolescents.

Primary and booster dose schedule adolescents and adults

The dosing schedule was studied in adolescents (11-17 years) in V72P10. Immune responses after 1, 2 and 3 doses given 1 or 2 months apart were studied. In addition, an extension of this study was presented during the assessment period, of a single booster dose given 6 months after the first primary vaccination. This is the only study in this age group and it was conducted in Chile.

The dosing schedule in adults was studied in V72P5 (three doses given a 0, 1, 2 months) immune responses measured after 2nd and 3rd dose) and in study V72P4 (three doses given at 0, 2, 6 months) included adults 18-50 years.

The primary immunogenicity results from studies V72P4, V72P5 and V72P10 are summarized in Table 18. Overall, the response rates are high to all strains.

Preliminary SBA data for NHBA using strain M10713 were submitted during the assessment period for study V72P10. The baseline titres were high and most subjects had SBA titres ≥1:5 before vaccination (Table 19). The titres increased somewhat after vaccination, but the clinical relevance of the increase is unclear. The Company suggested that the reason for the high baseline titres could be antibodies directed to cross-reacting antigens from other *N. meningitidis* strains or other Neisseria species, e.g. *N. lactamica*. The impact of vaccination with rMenB+OMV on the normal flora, especially *N. lactamica* should be further discussed. The possibility that the NHBA antigen elicits antibodies that cross-react with *N. lactamica* and possibly decreases carriage should be discussed. *N. lactamica* has been reported to inversely correlate to carriage of *N. meningitidis*, and may even protect against meningococcal disease.

In addition to the results shown in Table 18, percentages of responders using SBA titres ≥1:8, and percentages of subjects with 4-fold or greater titre increase were calculated in studies V72P5 andV72P10. The response rate in V72P10 was still high using SBA titres ≥1:8, ≥99% against all three strains after two doses.

A single dose resulted in overall lower response rates compared with the 2- and 3-dose regimens, supporting at least a 2-dose priming in this age group.

Data from a single booster dose given at month 6 in study V72P10 were presented during the assessment period. Data covering month 7 following the first dose were presented as well as responses to a single booster dose given at 6 months after the first dose (Table 20). These data indicate that the majority of subjects (at least 85%) have remaining bactericidal antibodies at study month 7 (i.e. 5-6 months after the last of the recommended 2 doses) to fHbp, NadA and PorA. Thus, there does not seem to be a need to vaccinate as soon as 6 months following the two primary doses. The GMTs following the booster dose were numerically higher than the GMTs following the two primary doses. The Applicant is planning further follow-up of study V72P10, extension study V72P10E1, which will cover an interval of 18 months to 22 months following the primary vaccination. The results of this study should be submitted when available. It would also be highly desirable to have a similar follow-up in a European adolescent population, to ensure that the provided data are relevant for the intended target population.

The results in adults are considered promising but very few subjects were included in the studies.

In conclusion, two doses have been shown to induce adequate immune responses to three of the vaccine antigens, fHbp, NadA and PorA. The response to NHBA demonstrated to be robust, although a large proportion of subjects had antibodies before vaccination. The antibody persistence beyond 6 months in adolescents is currently unknown, as well as the duration of immunogical memory.

Table 18 Immune Responses to rMenB+OMV NZ After a Two-dose Schedule in Adolescents and Adults (11 Years and Above) (PP Population)

Reference Strain	Age	18-40 yrs	11-17 yrs	18-50 yrs	11-17 yrs
		0,1 Schedule V72P5 (N=28)	0,1 Schedule V72P10 (N=639)	0,2 Schedule V72P4 (N=46)	0,2 Schedule V72P10 (N=320)
H44/76	% hSBA≥1:4/1:5[d] (95% CI)	28 (100%) (88; 100)	637 (100%) (99; 100) N=638	46 (100%) (92; 100)	319 (100%) (99: 100) N=319
	hSBA GMT (95% CI)	100 (75; 133)	210 (193; 229) N=638	93 (71: 121)	234 (209; 263) N=319
	hSBA GMR[e] (95% CI)	43 (25; 72)	54 (48; 61) N=637	38 (27; 53)	57 (48; 68) N=319
5/99	% hSBA≥1:4/1:5[d] (95% CI)	28 (100%) (88; 100)	638 (100%) (99; 100)	46 (100%) (92; 100)	318 (99%) (98; 100)
	hSBA GMT (95% CI)	566 (338; 948)	490 (455; 528)	144 (108; 193)	734 (653; 825)
	hSBA GMR[e] (95% CI)	139 (70; 277)	186 (166; 208) N=638	63 (44; 92)	280 (236; 332) N=320
NZ98/254	% hSBA≥1:4/1:5[d] (95% CI)	27 (96%) (82; 100)	637 (100%) (99; 100)	42 (91%) (79; 98)	319 (100%) (99; 100) N=319
	hSBA GMT (95% CI)	47 (30; 75)	92 (84; 102)	32 (21; 48)	123 (107; 142) N=319
	hSBA GMR[e] (95% CI)	27 (16; 48)	31 (28; 34) N=637	17 (12; 26)	39 (33; 47) N=319
Anti NHBA (287-953)	ELISA GMC (95% CI)	ND	3418 (2556; 4570) N=69	ND	3128 (2386; 4100) N=70
	ELISA GMR[e] (95% CI)	ND	87 (64; 120) N=66	ND	83 (59; 115) N=70

[d]cut-off used for hSBA titers was 1:4 in studies V72P4, V72P5, V72P9 and V72P10 and 1:5 in study V72P13E1; [e]GMT or GMC at one month after 2nd vaccination over baseline titers.

Table 19 Percentages (95% CI) of Subjects with hSBA ≥ 1:4 Against Strain M10713 After a Two-Dose Schedule of rMenB+OMV NZ in Adolescents Aged 11 to 17 Years – Study V72P10

		rMenB+OMV NZ Month 0, 1 Schedule	**rMenB+OMV NZ Month 0, 2 Schedule**
		N=46	**N=46**
Month 0(Baseline)	% hSBA≥1:4 (95% CI)	96% (85-99)	80% (66-91)
	hSBA GMT (95% CI)	32 (21-50)	30 (20-47)
1 Month After 2nd Dose	% hSBA≥1:4 (95% CI)	100% (92-100)	100% (92-100)
	hSBA GMT (95% CI)	99 (76-129)	107 (82-140)

Table 20: Percentages (95% CI) of Subjects with hSBA≥ 1:4 After Primary and Booster Vaccinations, by Strain – PP Population V72P10

		rMenB06	rMenB0	rMenB016	rMenB01	rMenB026	rMenB02	rMenB012	rMenB6
		N=112	N=223	N=113	N=231	N=110	N=232	N=334	N=116
Strain 44/76-SL	Month 0	42% (33-52)	47% (40-54)	41% (32-50)	38% (32-45)	37% (28-47)	47% (40-53)	46% (41-52)	46% (36-55)
	Month 1	**92% (85-96)**	**92% (88-95)**	95% (89-98)	93% (88-96)	90% (83-95)	92% (88-95)	95% (92-97) N=333	43% (34-53) N=115
	Month 2	88% (80-93) N=108	92% (88-95) N=213	**100% (97-100) N=108**	**100% (98-100) N=222**	88% (80-93) N=105	89% (85-93) N=219	100% (98-100) N=307	50% (40-59) N=109
	Month 3	84% (76-90) N=107	88% (82-92) N=208	99% (95-100) N=105	100% (97-100) N=215	**100% (97-100) N=104**	**100% (98-100) N=215**	**100% (98-100) N=303**	48% (38-58) N=108
	Month 6	76% (66-84) N=100	72% (65-79) N=188	93% (86-97) N=100	92% (88-96) N=198	97% (91-99) N=99	98% (94-99) N=201	97% (94-99) N=278	46% (36-56) N=100
	Month 7	**100% (96-100) N=86**	71% (64-78) N=173	**100% (96-100)** N=95	90% (85-94) N=186	**100% (96-100) N=91**	95% (91-98) N=179	95% (92-98) N=255	**93% (85-97) N=95**
		N=112	N=223	N=113	N=231	N=110	N=232	N=334	N=116
Strain 5/99	Month 0	29% (20-38)	41% (35-48)	28% (20-38)	31% (25-38)	30% (22-39)	37% (31-44)	36% (30-41)	29% (21-38)
	Month 1	**97% (92-99) N=111**	**96% (93-98)**	96% (90-99)	97% (94-99)	97% (92-99)	96% (93-98)	97% (94-98) N=333	35% (26-44) N=115
	Month 2	95% (90-98) N=108	94% (90-97) N=213	**100% (97-100) N=108**	**100% (98-100) N=222**	89% (81-94) N=105	95% (92-98) N=219	100% (98-100) N=308	31% (23-41) N=109
	Month 3	92% (85-96) N=107	89% (84-93) N=209	99% (95-100) N=105	100% (98-100) N=215	**98% (93-100) N=105**	**100% (98-100) N=215**	**100% (99-100) N=303**	32% (24-42) N=108
	Month 6	79% (70-87) N=100	74% (67-80) N=188	99% (95-100) N=100	98% (96-100) N=198	99% (95-100) N=99	100% (97-100) N=201	100% (98-100) N=278	28% (19-38) N=100
	Month 7	**99% (94-100) N=86**	67% (60-74) N=173	**100% (96-100) N=95**	98% (95-99) N=187	**100% (96-100) N=91**	99% (96-100) N=179	99% (97-100) N=255	**93% (85-97) N=95**
		N=112	N=223	N=113	N=231	N=110	N=232	N=333	N=116
Strain NZ98/254	Month 0	32% (24-42)	39% (33-46)	33% (24-42)	35% (29-41)	34% (25-43)	37% (31-44)	33% (28-38)	38% (29-47)
	Month 1	**90% (83-95) N=111**	**94% (90-97)**	95% (89-98)	94% (90-96)	90% (83-95)	93% (89-96)	95% (92-97)	38% (29-48) N=115

	rMenB06	rMenB0	rMenB016	rMenB01	rMenB026	rMenB02	rMenB012	rMenB6
Month 2	81% (73-88) N=107	84% (78-88) N=213	**99%** **(95-100)** **N=108**	**100%** **(98-100)** **N=222**	78% (69-86) N=105	85% (79-89) N=218	100% (98-100) N=308	39% (29-48) N=109
Month 3	80% (72-87) N=107	76% (70-82) N=208	97% (92-99) N=105	97% (94-99) N=215	**100%** **(97-100)** **N=104**	**100%** **(98-100)** **N=215**	**99%** **(97-100)** **N=302**	43% (33-52) N=108
Month 6	81% (72-88) N=99	69% (62-76) N=188	93% (86-97) N=100	89% (84-93) N=198	97% (91-99) N=99	96% (92-98) N=200	97% (94-99) N=278	45% (35-55) N=100
Month 7	**100%** **(96-100)** **N=86**	67% (60-74) N=172	**100%** **(96-100)** **N=95**	85% (79-90) N=187	**100%** **(96-100)** **N=91**	94% (89-97) N=179	95% (92-98) N=255	**93%** **(85-97)** **N=95**

Supportive studies

Study V72P4

A Phase 2, Multi-Center, Open-label Study of the Safety, Tolerability and Immunogenicity of Novartis Meningococcal B Recombinant Vaccine When Administered at a 0, 2, 6-Month Schedule and of a Single dose of Novartis Meningococcal ACWY Conjugate Vaccine in Healthy At-risk Adults 18-50 Years of Age

Methodology

This was a Phase 2, open-label, multi-center study in healthy at-risk adults routinely exposed to *N. meningitidis*. Novartis rMenB + OMV (0.5 mL each dose) was to be administered intramuscularly (IM) according to a 0, 2, 6-month immunization schedule. A single dose (0.5 mL) of Novartis MenACWY conjugate vaccine was to be administered at study month 7. Blood samples were obtained for meningococcal serology from all subjects at baseline, one month post-first rMenB + OMV vaccination, one month post-second rMenB + OMV vaccination, pre-and one month post-third rMenB + OMV vaccination and one month post-MenACWY vaccination.

Objectives:

Immunogenicity

To explore the immunogenicity of three doses of Novartis rMenB + OMV in healthy at-risk adults, by evaluation of the breadth of serum bactericidal activity using human complement (SBA) response against a panel of genetically distinct meningococcal strains, at one month after the administration of the first, the second and the third dose and immediately before the administration of the third dose.

Immunogenicity results

Of the total of 54 subjects enrolled, 53 were vaccinated and 48 subjects completed the study. The immunogenicity analysis for rMenB + OMV was performed on the per protocol (PP) population which included 46 (85%) subjects.

Immunogenicity of three of the major vaccine antigens in the rMenB+OMV vaccine, as measured by SBA, was determined using a panel of three meningococcal serogroup B reference strains.

Table 21 Percentages (95%CI) of Subjects with Bactericidal Titers ≥1:4, by *N. meningitidis* Serogroup B Strain

	Strain 44/76-SL N=46	Strain 5/99 N=46	Strain NZ98/254 N=46
Baseline	17 (37%) (23-52)	17 (37%) (23-52)	10 (22%) (11-36)
1 Month Post 1st Vacc.	21 (84%) (64-95) N=25	22 (88%) (69-97) N=25	20 (80%) (59-93) N=25
1 Month Post 2nd Vacc.	46 (100%) (92-100)	46 (100%) (92-100)	42 (91%) (79-98)
4 Mos Post 2nd/Pre 3rd	23 (96%) (79-100) N=24	24 (100%) (86-100) N=24	16 (67%) (45-84) N=24
1 Month Post 3rd Vacc.	38 (97%) (87-100) N=39	39 (100%) (91-100) N=39	36 (92%) (79-98) N=39

Four studies were conducted using an early formulation consisting of the OMV component based on the Norwegian strain H44/76 plus the recombinant proteins present in Bexsero. The early studies were all conducted in the US. The results of these studies are generally confirmed in later studies with the final formulation.

Additional analysis submitted

Primary dose schedule infants:

Different dosing schedules in infants were used in studies V72P12 and V72P16 (three doses 1-2 months apart) and V72P6 (three doses two months apart, immune responses measured after 2nd and 3rd doses). In the phase III study V72P13 the 2, 4, 6 months schedule was used.

The SBA responses to fHbp, NadA and PorA and ELISA responses to NHBA after three priming doses given at 2, 4, 6 or 2, 3, 4 months of age in studies V72P6, V72P12,V72P13 and V72P16 are summarized in Table 22. The results from study V72P6 were generally lower than the results from the larger studies V72P12 and V72P13.

Table 22 Immune Responses to rMenB+OMV NZ After a Three-dose Primary Schedule in Infants from 2 Months of Age with and without Concomitant Routine Infant Vaccines (PP population)

		V72P13	V72P12			V72P6	V72P16
Reference Strain		2,4,6 with concomitant routine vaccinations	2,4,6 with concomitant routine vaccinations	2,4,6 with 3,5,7 routine vaccinations	2,3,4 with concomitant routine vaccinations	2,4,6 with concomitant routine vaccinations	2, 3, 4 with concomitant routine vaccinations
H44/76	% hSBA≥1:5 (95% CI)	1146 (100%) (99-100) N=1149	523 (100%) (99-100) N=525	532 (100%) (99-100) N=534	271 (99%) (97-100) N=273	34 (87%) (73; 96) N=39	169 (100%) (98; 100) N=169
	hSBA GMT (95%CI)	91 (87-95) N=1149	86 (80-92) N=525	113 (105-121) N=534	82 (75-91) N=273	30 (19; 46) N=39	100 (90; 112) N=169
	hSBA GMR [a] (95% CI)	79 (75-84) N=1098	58 (52-64) N=501	83 (74-92) N=507	61 (53-70) N=262	21 (13; 34) N=39	80 (69; 93) N=156
5/99	% hSBA≥1:5 (95% CI)	1149 (100%) (99-100) N=1152	526 (100%) (99-100) N=527	526 (99%) (98-100) N=529	275 (100%) (99-100) N=275	35 (95%) (82; 99) N=37	163 (99%) (97; 100) N=164
	hSBA GMT (95%CI)	635 (606-665) N=1152	537 (494-584) N=527	699 (643-759) N=529	325 (292-362) N=275	126 (77; 205) N=37	393 (344; 448) N=164
	hSBA GMR [a] (95% CI)	537 (505-572) N=1098	430 (379-487) N=497	553 (489-625) N=494	271 (231-318) N=257	19 (13; 34) N=39	345 (291; 407) N=151
NZ98/254	% hSBA≥1:5 (95% CI)	965 (84%) (82-86) N=1152	421 (79%) (76-83) N=530	467 (87%) (84-90) N=534	223 (81%) (76-86) N=274	34 (85%) (70; 94) N=40	133 (78%) (71;84) N=170
	hSBA GMT (95%CI)	14 (13-15) N=1152	12 (11-14) N=530	18 (16-20) N=534	11 (9.14-12) N=274	19 (11; 33) N=40	9.91 (8.48; 12) N=170
	hSBA GMR [a] (95% CI)	14 (13-15) N=1102	11 (9.28-12) N=504	16 (14-19) N=503	10 (8.52-12) N=258	16 (9.4; 28) N=40	9.45 (8.02; 11) N=161
Anti NHBA (287-953)	ELISA GMC (95%CI)	3370 (3270-3472) N=1823	3327 (3115-3553) N=545	4244 (3978-4527) N=557	3254 (2988-3545) N=281	Not done.	Not done.
	ELISA GMR [a] (95%CI)	156 (150-162) N=1754	149 (136-164) N=531	190 (173-208) N=539	145 (128-164) N=275	Not done.	Not done.

[a]GMT or GMC at one month after 3rd vaccination over baseline titers

In addition to the results shown in Table 22, the percentage of responders using SBA titres ≥8, and percentage of subjects with 4-fold or greater titre increase were calculated in studies V72P6 and V72P13 for fHbp, NadA and PorA. The response rate in the phase III study V72P13 was still high using SBA titres ≥1:8, 72% against NZ98/254 and 100% against the other two strains.

Immune responses to five additional strains were also presented in V72P6. The additional strains were selected because 1) they are strains which vary in their vaccine antigen composition and/or expression and 2) are representative of the major disease causing types currently in the UK. In addition, serogroup B strain LNP 20404, a clinical isolate from a recent outbreak in Normandy, France was also used. Of the five additional strains baseline titres against one strain, GB101, where quite high, and did not increase substantially after two or three doses. No responses were observed against strain GB355, as expected as this strain does not express any of the vaccine antigens. The responses against GB364 were modest, while the responses against UKP1.7-2,4 and LNP20404 were more robust after vaccination with the OMV-containing vaccine.

In study V72P6 SBA responses to fHbp, NadA and PorA were measured after the second and third vaccine dose. The third dose did not increase the response rate compared to the second dose for strains 5/99 and H44/76. For strain NZ 98/254 the response rate increased from 74% to 85%, with overlapping 95% CI. The SBA measures both IgG and IgM antibodies, and one explanation for the similar responses after two and three doses could be that the first doses induce a predominant IgM response, which declines and is later replace with IgG responses. However, no ELISA data are available for this population. Further data on two priming doses in infants are not available.

The SBA GMTs to the 2, 3, 4 month schedule were slightly lower than following the 2, 4, 6 months schedule for strains 5/99 in study V72P12. However, the percentage of subjects with SBA titres ≥1:5 were very similar between the two groups. Data from the extension study V72P12E1 were summarised in the response to the Day 120 LoQ. Immunogenicity data for antibody persistence and the booster dose at 12 months of age were presented. At 12 months of age, there was a trend for bactericidal antibody persistence to be slightly higher for the 2, 4, 6 compared to the 2, 3, 4-month schedule; some of this difference can be attributed to the longer time interval from the last vaccination for the 2, 3, 4 schedule (8 months vs. 6 months for the 2, 4, 6 month schedule) and thus longer time period for antibodies to decay. The pre-booster titres were very low to strain NZ98/254 in both groups.

The primary immune responses in infants to NHBA were measured in study V72P13, using strain M10713 in a subset of 100 subjects as shown in Table 23. These results indicate a good primary response rate to the NHBA antigen, although the baseline titres were comparatively high. In addition, hSBA data using strain M10713 were presented in response to the Day 120 LoQ from study V72P16. The responses were modest to the NHBA antigen, which caused some concern. The low hSBA response to NHBA after 3 primary doses according to the 2, 3, 4 month schedule was also seen in V72P12 (E1). Even though the level of bactericidal antibodies against NHBA is very low after 3 doses according to the 2, 3, 4, month scheme, the good response after a booster dose at 12 month of age demonstrates that priming has been achieved during the three primary doses.

Table 23 Number (Percentage)(95% CI) of Subjects with hSBA Titers≥ 1:5 Against Reference Strain M10713, Studies V72P13 and V72P13E1 in Infants and Toddlers, MITT populations.

Vaccinations given at Age in Months	(Month 0) Baseline	1-mth Post-3rd Vacc	6-mths Post-3rd Vacc (Pre-Booster)	1 mth Post-Booster
rMenB+OMV NZ +Infanrix Hexa, Prevenar at 2,4,and 6; booster at 12	33 (33%) (24-43)	84 (84%) (75-91)	61 (61%) (51-71)	98 (98%) (93-100)
Priorix-Tetra (MMR) at 12 or 13	N=100	N=100	N=100	N=100

In summary three doses to infants according to 2, 4, 6 or 2, 3, 4 month schedule is considered adequately supported by the data. The exception is the bactericidal responses to NHBA antigen in the 2, 3, 4 month schedule where a low percentage of subjects are considered protected until the booster dose is administered at 12-23 months.

Primary dose schedule in older infants and children:

Dose schedule in older unvaccinated infants, 6-8 months of age was studied in V72P9, (2 doses were given 2 months apart with a third dose around 12 months of age). Unvaccinated children were vaccinated with 2 doses at 12+14 months of age in study V72P13E1.

The results two vaccine doses given two months apart in studies V72P9 and V72P3E1 are summarized in Table 24.

Table 24 Immune Responses to rMenB+OMV NZ After a Two-dose Schedule in Older Infants and in Toddlers (from 6 Months of Age) – (PP Population)

Reference Strain	**Age**	**12-15 months**		**6-8 months**
		12M13B15B V72P13E1[b] N=163	**12M12B14B V72P13E1[c] N=67**	**0,2 Schedule[a] V72P9 (N=24)**
H44/76	% hSBA≥1:4/1:5[d] (95% CI)	163 (100%) (98-100)	67 (100%) (95-100)	23 (100%) (85-100)
	hSBA GMT (95% CI)	271 (237-310)	248 (201-306)	250 (173-361) N=23
	hSBA GMR[e] (95% CI)	217 (185-255) N=159	203 (158-261) N=66	144 (101-204) N=23
5/99	% hSBA≥1:4/1:5[d] (95% CI)	164 (100%) (98-100) N=164	67 (100%) (95-100)	23 (100%) (85-100)
	hSBA GMT (95% CI)	599 (520-690)	627 (502-783)	534 (395-721) N=23

	hSBA GMR [e] (95% CI)	560 (478-656) N=159	620 (485-793) N=66	509 (381-680) N=23
NZ98/254	% hSBA≥1:4/1:5[d] (95% CI)	164 (100%) (98-100) N=164	65 (96%) (88-99) N=68	21 (95%) (77-100)
	hSBA GMT (95% CI)	43 (38-49)	31 (25-38) N=67	27 (21-36) N=22
	hSBA GMR [e] (95% CI)	43 (37-49) N=161	31 (25-38) N=67	27 (21-36) N=22
Anti NHBA (287-953)	ELISA GMC (95% CI)	5698 (5030-6454) N=165	7154 (5880-8704) N=68	2912 (2178-3894) N=23
	ELISA GMR [e] (95% CI)	279 (245-317) N=162	326 (259-410) N=66	139 (102-191) N=23
Anti NHBA (287-953)	% hSBA≥1:5 (95% CI)	63% (48-77) N=29/46	74% (59-86) N=32/43	NA
	hSBA GMT (95% CI)	11 (7.07-16) N=46	15 (9.7-23) N=43	NA

[a]subjects who received rMenB+OMV NZ at 6 and 8 months of age; [b]subjects who received routine vaccinations only in study V72P13 at 2,4,6 months and were administered MMRV at 12 months and rMenB+OMV NZ at 13 and 15 months in the extension V72P13E1; [c]subjects who received routine vaccinations only in study V72P13 at 2,4,6 months and were administered rMenB+OMV NZ concomitantly with MMRV at 12 months and rMenB+OMV NZ alone at 14 months in the extension V72P13E1; [d]cut-off used for hSBA titers was 1:4 in studies V72P4, V72P5, V72P9 and V72P10 and 1:5 in study V72P13E1; [e]GMT or GMC at one month after 2nd vaccination over baseline titers.

The results presented in Table 24 were supported by data on percentages of subjects achieving SBA titres ≥1:8 in study V72P9 (96%, 100%, and 91% respectively against fHbp, NadA and PorA). In addition immune responses to four additional strains were also presented in V72P9. The responses were high against 3 of the four strains, and no responses were expected against the fourth strain which did not express any vaccine antigen.

The SBA responses to NHBA in study V72P13E1 were presented in response to the Day 120 LoQ. In this study 20% and 16% of the subjects in the receiving the rMenB+OMV vaccine at 13, 15 and 12, 14 months schedule, had SBA titres ≥1:5. As shown in the amended Table 25 below, the response rates 1 month after the second dose were 63% and 74% respectively. This response was lower than the response to a single booster dose in the same age group (98% response rate) and lower than the responses to the other three antigens.

The responses reported in study V72P9 were generally lower than the response in study V72P13E1.

Overall, the response rates and GMTs were considered acceptable and in line with the responses in other age groups except the responses to NHBA.

Booster vaccinations –infants and toddlers

A single booster dose at 12 months of age after 3 priming infant vaccinations was studied in V72P6, V72P12E1 and V72P13E1. In study V72P9 a single booster dose was given at twelve months of age following 2 primary vaccinations at 6 and 8 months. Thus, data on booster vaccinations after 2 dose priming infants from 2 months of age has not been studied.

The immune responses to a single booster dose given at 12 months of age in study V72P13E1 and V72P9 are summarized in Table 25. The results of study V72P6 are not shown in this overview, but were slightly lower than what is shown in study V72P13E1. See also results from primary vaccination in these studies in Table 22 above.

Table 25 Immune Responses to a Booster Vaccination[a] with rMenB+OMV NZ at 12 Months of Age – (PP Population).

Reference Strain		**V72P13E1[b] In toddlers who had received rMenB+OMV NZ with routine vaccines at 2,4,6 months**						**V72P9 In toddlers who received rMenB+OMV NZ at 6,8 months**	
		% hSBA ≥1:5 (95%CI)		**hSBA GMT (95%CI)**		**hSBA GMR (95%CI)**		**% hSBA ≥1:4 (95%CI)**	**hSBA GMT (95%CI)**
		12B12M (1a)	**12B13M (1b)**	**12B12M (1a)**	**12B13M (1b)**	**12B12M (1a)**	**12B13M (1b)**	**MenB**	**MenB**
H44/76	Baseline[c]	171 (81%) (75-86) N=211	177 (82%) (77-87) N=215	11 (9.27-12) N=211	10 (9.11-12) N=215	-	-	ND	ND
	1 Month After Booster	210 (100%) (98-100) N=210	212 (100%) (98-100) N=212	139 (123-156) N = 210	119 (105-133) N = 212	13 (12-14) N=207	11 (10-13) N=209	24 (100%) (86-100) N=24	189 (136-263) N=24
5/99	Baseline[c]	206 (98%) (95-99) N=210	212 (100%) (97-100) N=213	81 (71-93) N=210	81 (71-92) N=213	-	-	ND	ND
	1 Month After Booster	209 (100%) (98-100) N=209	212 (100%) (98-100) N=212	1503 (1339-1686) N = 209	1429 (1274-1603) N = 212	18 (16-21) N=205	18 (16-20) N=207	24 (100%) (86-100) N=24	906 (700-1172) N=24
NZ98/254	Baseline[c]	41 (19%) (14-25) N=211	52 (24%) (19-30) N=215	2.07 (1.8-2.38) N=211	2.21 (1.92-2.55) N=215	-	-	ND	ND
	1 Month After Booster	204 (97%) (93-99) N=211	200 (94%) (90-97) N=213	39 (33-46) N=211	32 (27-37) N = 213	19 (16-22) N=208	15 (12-17) N=210	23 (96%) (79-100) N=24	44 (32-62) N=24
		-	-	**ELISA GMC (95%CI)**		**ELISA GMR (95%CI)**		-	**ELISA GMC (95%CI)**
Anti NHBA (287-953)	Baseline[c]	-	-	390 (351-433) N=212	389 (349-434) N=216	-	-	-	-
	1 Month After Booster	-	-	6225 (5571-6956) N=213	5608 (5111-6154) N=214	16 (14-18) N=211	14 (13-16) N=212	-	3521 (2739-4527) N=25

[a] 4th dose in study V72P13E1 and 3rd dose in study V/2P9; [b] **12B12M(1a) =** in the open-label (immunogenicity) subset of V72P13, these subjects had received rMenB+OMV NZ + routine vaccinations at 2, 4 and 6 months of age. In V72P13E1, these subjects received a rMenB+OMV NZ booster and MMRV at 12 months of age; **12B13M(1b) =** in the open-label (immunogenicity) subset of V72P13, these subjects had received rMenB+OMV NZ + routine vaccinations at 2, 4 and 6 months of age. In V72P13E1, these subjects received a rMenB+OMV NZ booster at 12 months of age and MMRV at 13 months of age; [c] Baseline= blood sample taken just before the booster vaccination

In study V72P12E1 a single booster dose was given to subjects receiving primary vaccinations at 2, 4, 6 months or 2, 3, 4 months. The booster responses were robust and similar for the two schedules for fHbp, NadA and PorA, demonstrating that the 2, 3, 4-month accelerated schedule was able to prime the infants for a booster response as well as the 2, 4, 6-month schedule. The responses were also in agreement with the results from study V72P13E1.

Although no direct comparison of responses to a booster dose given at 12 months between infants receiving 3 doses and older infants given 2 doses is available, the SBA GMTs in study V72P9 after the dose given at 12 months were higher than in study V72P6 (also performed in the UK) but slightly lower than the results of V72P13E1. The interval between dose 1 and 2 in V72P9 was on average 58 and 59 days, and between dose 2 and 3 85 and 83 days in the two groups respectively, thus the three doses were actually given at age 7, 9 and 12 months.

The responses to a single booster dose at 12 months of age were considerably higher than the responses to a single dose given to naïve subjects in study V72P13E1. The responses to the booster dose in V72P13E1 were also higher compared to the responses to the third priming dose given at 6 months of age in V72P13 (tables 3 and 6) for fHbp, NadA and PorA.

Booster responses to NHBA in toddlers were also demonstrated using SBA in V72P13E1.

The baseline data indicate that the immune responses after the primary doses decline over the 6 month interval, and particularly for the OMV component the decline is substantial (Table 26).

Taken together, these results indicate that immunological memory is induced by the three priming doses given at 2, 4, 6 or 2, 3, 4 months of age and by 2 doses given from 6 months of age.

The immune responses up to 12 months after the 4th dose were studied in V72P13E2. The responses to fHbp and NadA were still high, while the responses to NHBA and OMV had decreased to very low levels (Table 27), suggesting the need for a further booster dose from 12 months to 23 months after the primary series.

Table 26 Immune Responses to a Booster Vaccinationa with rMenB+OMV NZ at 12 Months of Age – (PP Population).

Reference Strain		V72P13E1[b] In toddlers who had received rMenB+OMV NZ with routine vaccines at 2,4,6 months						V72P9 In toddlers who received rMenB+OMV NZ at 6,8 months	
		% hSBA ≥1:5 (95%CI)		hSBA GMT (95% CI)		hSBA GMR (95% CI)		% hSBA ≥1:4 (95% CI)	hSBA GMT (95% CI)
		12B12M (1a)	12B13M (1b)	12B12M (1a)	12B13M (1b)	12B12M (1a)	12B13M (1b)	MenB	MenB
H44/76	Baseline[c]	171 (81%) (75-86) N=211	177 (82%) (77-87) N=215	11 (9.27-12) N=211	10 (9.11-12) N=215	-	-	ND	ND
	1 Month After Booster	210 (100%) (98-100) N=210	212 (100%) (98-100) N=212	139 (123-156) N = 210	119 (105-133) N = 212	13 (12-14) N=207	11 (10-13) N=209	24 (100%) (86-100) N=24	189 (136-263) N=24
5/99	Baseline[c]	206 (98%) (95-99) N=210	212 (100%) (97-100) N=213	81 (71-93) N=210	81 (71-92) N=213	-	-	ND	ND
	1 Month After Booster	209 (100%) (98-100) N=209	212 (100%) (98-100) N=212	1503 (1339-1686) N = 209	1429 (1274-1603) N = 212	18 (16-21) N=205	18 (16-20) N=207	24 (100%) (86-100) N=24	906 (700-1172) N=24
NZ98/254	Baseline[c]	41 (19%) (14-25) N=211	52 (24%) (19-30) N=215	2.07 (1.8-2.38) N=211	2.21 (1.92-2.55) N=215	-	-	ND	ND
	1 Month After Booster	204 (97%) (93-99) N=211	200 (94%) (90-97) N=213	39 (33-46) N=211	32 (27-37) N = 213	19 (16-22) N=208	15 (12-17) N=210	23 (96%) (79-100) N=24	44 (32-62) N=24
		-	-	ELISA GMC (95% CI)		ELISA GMR (95% CI)		-	ELISA GMC (95% CI)
Anti NHBA (287-953)	Baseline[c]	-	-	390 (351-433) N=212	389 (349-434) N=216	-	-	-	-
	1 Month After Booster	-	-	6225 (5571-6956) N=213	5608 (5111-6154) N=214	16 (14-18) N=211	14 (13-16) N=212	-	3521 (2739-4527) N=25

[a]4[th] dose in study V72P13E1 and 3[rd] dose in study V/2P9; [b]**12B12M(1a) =** in the open-label (immunogenicity) subset of V72P13, these subjects had received rMenB+OMV NZ + routine vaccinations at 2, 4 and 6 months of age. In V72P13E1, these subjects received a rMenB+OMV NZ booster and MMRV at 12 months of age; 12B13M(1b) **=** in the open-label (immunogenicity) subset of V72P13, these subjects had received rMenB+OMV NZ + routine vaccinations at 2, 4 and 6 months of age. In V72P13E1, these subjects received a rMenB+OMV NZ booster at 12 months of age and MMRV at 13 months of age; [c]Baseline= blood sample taken just before the booster vaccination

Table 27 Percentage of Subjects with hSBA ≥1:5 at 12 months post-booster dose in study V72P13E2

SBA target strain	rMenB+OMV at 2, 4, 6, 12 months
HH44/76	185 (**62**%) (56%; 67%) N=299
5/99	290 (**97**%) (95%; 99%) N=298
NZ98/254	52 (**17**%) (13%; 22%) N=300
M10713	105 (**36**%) (31%; 42%)

Primary vaccination in children 2-10 years

Currently data are available from studies V72P13E2, V72P12E1, V72P9E1 and V72P6E1 in children 2-11 years. In these studies two doses were given two months apart. Overall the immune responses in this age group are considered satisfactory.

Table 28 Bactericidal Responses Following a Two-Dose Schedule of rMenB+OMV NZ in Unvaccinated Children 24 to 26 Months of Age (Studies V72P12E1 and V72P13E2) and 40 to 44 Months of Age (Studies V72P6E1 and V72P9E1)

Age of subjects			**24 to 26 months**		**40-44 months**	
Reference Strain (Antigen) Time Point / Immunogenicity Outcome			Study V72P12E1	Study V72P13E2	Study V72P6E1	Study V72P9E1
Strain H44/76 (fHBP)	Baseline	% hSBA ≥1:4 or ≥1:5* (95% CI)	4% (0-13) N=55	3% (1-8) N=112	63% (46-77) N=40	3% (0.065-13) N=39
		hSBA GMT (95%CI)	1.03 (0.82-1.31) N=55	1.17 (1.06-1.28) N=112	4.25 (3.22-5.6) N=40	1.08 (0.97-1.2) N=39
	Post 2nd Dose	% hSBA ≥1:4 or ≥1:5* (95% CI)	100% (93-100) N=50	100% (97-100) N=105	100% (90-100) N=36	100% (88-100) N=30
		hSBA GMT (95%CI)	174 (138-221) N=50	220 (186-261) N=105	88 (66-117) N=36	74 (57-94) N=30
		hSBA GMR (95% CI)	161 (116-224) N=50	187 (156-224) N=105	20 (15-28) N=34	66 (49-90) N=29
Strain 5/99 (NadA)	Baseline	% hSBA ≥1:4 or ≥1:5* (95% CI)	2% (0.049-10) N=52	1% (0.023-5) N=110	3% (0.063-13) N=40	0% (0-9) N=40
		hSBA GMT (95%CI)	1.11 (0.92-1.33) N=52	1.04 (0.99-1.09) N=110	1.11 (0.9-1.36) N=40	1 (1-1) N=40
	Post 2nd Dose	% hSBA ≥1:4 or ≥1:5* (95% CI)	100% (93-100) N=50	99% (95-100) N=103	100% (90-100) N=36	100% (89-100) N=31
		hSBA GMT (95%CI)	601 (454-796) N=50	455 (372-556) N=103	1019 (762-1362) N=36	247 (188-323) N=31
		hSBA GMR (95% CI)	496 (369-666) N=48	433 (350-536) N=101	910 (594-1394) N=34	247 (188-323) N=31
Strain NZ98/254 (PorA P1.4)	Baseline	% hSBA ≥1:4 or ≥1:5* (95% CI)	4% (0-13) N=55	0% (0-3) N=112	0% (0-9) N=40	0% (0-9) N=39
		hSBA GMT (95%CI)	1.08 (0.99-1.19) N=55	1.01 (0.99-1.03) N=112	1 (1-1) N=40	1 (1-1) N=39
	Post 2nd Dose	% hSBA ≥1:4 or ≥1:5* (95% CI)	92% (80-98) N=49	98% (93-100) N=108	94% (81-99) N=36	90% (74-98) N=31
		hSBA GMT (95%CI	25 (19-32) N=49	27 (23-32) N=108	47 (31-72) N=36	16 (11-23) N=31
		hSBA GMR (95% CI)	22 (17-29) N=49	27 (23-32) N=108	47 (31-74) N=34	16 (11-23) N=30
Strain M10713 (NHBA)	Baseline	% hSBA ≥1:4 or ≥1:5* (95% CI)	16% (6-29) N=45	26% (18-35) N=109	68% (51-81) N=40	53% (36-68) N=40
		hSBA GMT (95%CI)	1.96 (1.17-3.28) N=45	2.32 (1.89-2.85) N=109	8.75 (5.22-15) N=40	4.82 (2.9-8) N=40
		% hSBA ≥1:4 or ≥1:5* (95%	82% (67-92) N=44	97% (91-99) N=100	89% (74-97) N=36	72% (53-87) N=29

	Post 2nd Dose	CI)				
		hSBA GMT (95%CI	21 (13-34) N=44	38 (32-45) N=100	33 (22-51) N=36	8.91 (5.19-15) N=29
		hSBA GMR (95% CI)	9.06 (5.39-15) N=41	16 (12-22) N=99	3.94 (2.14-7.25) N=34	1.9 (1.12-3.22) N=29

Immune response data to the NHBA Antigen

The available NHBA immunogenicity data, including hSBA data using M10713 as the indicator strain as well as ELISA data against the 287-953 vaccine antigen, are summarized below.

Infants: Three-Dose Primary Series Starting at 2 Months of Age with a Booster at 12 Months of Age

In studies V72P13, V72P12 and V72P16, bactericidal activity against strain M10713 was evaluated in subsets of infants receiving three primary doses of rMenB+OMV NZ co-administered with routine vaccines at either 2, 4 and 6 or 2, 3 and 4 months of age. The response prior to and one month following a fourth or booster dose given at 12 months of age was also evaluated in extension studies V72P13E1 and V72P12E1, and in study V72P16; and one year bactericidal antibody persistence post-boost was assessed in extension study V72P13E2. The percentage of subjects achieving hSBA ≥1:5 and hSBA GMTs are presented below in Table 29 and Table 30, respectively.

Prior to vaccination at 2 months of age and presumably representing residual maternal antibodies, the percentages of subjects with hSBA ≥1:5 against strain M10713 ranged from 33% to 53% across the three rMenB+OMV NZ groups and two control groups. In study V72P13, following rMenB+OMV NZ vaccinations at 2, 4 and 6 months of age, the percentages of subjects with hSBA ≥1:5 increased to 84% one month after the third vaccination, with 63% of subjects maintaining hSBA ≥1:5 at 12 months of age, indicating good persistence of bactericidal activity at this time point (Table 29). As shown in Table 30, hSBA GMTs increased significantly from a baseline value of 3.15 to 16 one month after the third vaccination, with bactericidal antibodies persisting at 12 months of age at a GMT of 8.4.

One month after the fourth or booster dose administered at 12 months of age (Table 29, study V72P13E1), the percentage of subjects achieving an hSBA titer of 1:5 or greater increased to 97%, and hSBA GMTs increased from a pre-booster GMT of 8.22 to a post-booster GMT of 37, demonstrating a robust bactericidal response to strain M10713. At 12 months after the booster vaccination, the percentage of subjects with hSBA ≥1:5 was 36% (95% CI: 31%-42%, Table 29, study V72P13E2), which was slightly higher than the baseline of a newly-recruited control group of unvaccinated subjects of similar age (26%, 95% CI: 18%-35%. This difference was also reflected in slightly higher hSBA GMTs for the rMenB+OMV NZ vaccinees (Table 30: rMenB+OMV NZ group – GMT of 3.35 [95% CI: 2.88-3.9] vs. control group – GMT 2.32 [1.89-2.85].

Following vaccinations with rMenB+OMV NZ at the accelerated 2, 3, 4-month schedule in studies V72P12 and V72P16, percentages of subjects with hSBA ≥1:5 at one month after the third vaccination were only slightly higher than the percentages at baseline. By comparison to the responses in the two control groups after the third vaccination, which takes into account the decay of maternal antibodies, modest antibody responses could be demonstrated in rMenB+OMV NZ vaccinees (Table 29, study V72P12 - 37% vs. 6%, study V72P16 - 43% vs. 20%).%). These results were consistent with the hSBA GMT data (Table 30), which showed slightly higher hSBA GMTs in the rMenB+OMV NZ vaccinees compared to those of the control subjects after the third vaccination. In extension study V72P12E1, a booster response was observed after the fourth dose of rMenB+OMV NZ with 74% of the subjects achieving a titer of 1:5 or greater; GMTs increased from a pre-booster level of 2.23 to 11 one month after the boost. Similar booster responses were observed in subjects administered a fourth dose of rMenB+OMV NZ at 12 months of age in study V72P16 (percentage of subjects

with hSBA ≥1:5: 72% vs. 26% for control group receiving their first dose of rMenB+OMV NZ at 12 months of age, Table 29 ; hSBA GMTs: 16 vs. 2.94 for control group, Table 30).

Table 29 Percentages (95% CI) of Subjects with hSBA ≥ 1:5 Against Strain M10713 After Primary Vaccination with rMenB+OMV NZ at Either 2, 4, 6 or 2, 3, 4 Months of Age with a Booster Dose at 12 Months of Age in Selected Groups

	Studies V72P13 / V72P13E1 / V72P13E2	**Studies V72P12 / V72P12E1**		**Study V72P16**	
	rMenB+OMV NZ 2, 4, 6, 12 Month Schedule	**rMenB+OMV NZ 2, 3, 4, 12 Month Schedule**	**Control Group* 2, 3, 4 Month Schedule**	**rMenB+OMV NZ 2, 3, 4, 12 Month Schedule**	**Control Group⁺ 2, 3, 4 Month Schedule**
Month 0 (Baseline)	33% (24-43) N=100	36% (27-45) N=112	44% (22-69) N=18	37% (20-56) N=30	53% (27-79) N=15
1 Month After 3rd Dose	84% (75-91) N=100	37% (28-46) N=112	6% (0-27) N=18	43% (26-61) N=35	20% (4-48) N=15
Pre-Booster	63% (50-75) N=65	24% (14-35) N=72	24% (8-47) N=21	24% (16-34) N=95	18% (11-27) N=97
1 Month After 4th Dose Boost	97% (89-100) N=65	74% (62-84) N=70	-	72% (61-80) N=95	26% (17-36) N=93
12 Months After 4th Dose Boost	36%^ (31-42) N=291	-	-	-	-

All MITT populations.
*Control group in Study V72P12 received routine vaccines only (InfanrixHexa, Prevenar) at 2, 3 and 4 months of age.
⁺Control group in Study V72P16 received MenC conjugate with routine vaccines (InfanrixHexa, Prevenar) at 2, 3 and 4 months of age. At 12 months of age, these subjects received the first of two doses of rMenB+OMV NZ. Following the first dose, the percentage of subjects with hSBA ≥1:5 against strain M10713 was 26% (95% CI: 17%-36%), N=24/93.
^Persistence of bactericidal activity was evaluated by comparing to the baseline of a newly recruited control group, which consisted of unvaccinated subjects approx. 24 months of age. At baseline, the percentage of subjects with hSBA ≥1:5 against strain M10713 was 26% (95% CI: 18%-35%), N=28/109.

Table 30 hSBA GMTs Against Strain M10713 After Primary Vaccination with rMenB+OMV NZ at Either 2, 4, 6 or 2, 3, 4 Months of Age with a Booster Dose at 12 Months of Age in Selected Groups

	Studies V72P13 / V72P13E1 / V72P13E2	Studies V72P12 / V72P12E1		Study V72P16	
	rMenB+OMV NZ 2, 4, 6, 12 Month Schedule	rMenB+OMV NZ 2, 3, 4, 12 Month Schedule	Control Group* 2, 3, 4 Month Schedule	rMenB+OMV NZ 2, 3, 4, 12 Month Schedule	Control Group+ 2, 3, 4 Month Schedule
Month 0 (Baseline)	3.15 (2.5-3.98) N=100	3.51 (2.72-4.53) N=112	3.91 (2-7.65) N=18	3.28 (1.78-6.03) N=30	4.08 (1.93-8.62) N=15
1 Month After 3rd Dose	16 (13-21) N=100	3.24 (2.49-4.21) N=112	1.36 (1.04-1.78) N=18	3.29 (1.85-5.83) N=35	2.21 (1.3-3.76) N=15
Pre-Booster	8.22 (5.87-12) N=100	2.23 (1.68-2.96) N=72	2.5 (1.47-4.24) N=21	1.89 (1.4-2.55) N=95	1.79 (1.48-2.17) N=97
1 Month After 4th Dose Boost	37 (29-46) N=65	11 (8.31-16) N=70	-	16 (10-24) N=95	2.94 (2.26-3.82) N=93
12 Months After 4th Dose Boost	3.35^ (2.88-3.9) N=291	-	-	-	-

All MITT populations.
*Control group in Study V72P12 received routine vaccines only (InfanrixHexa, Prevenar) at 2, 3 and 4 months of age.
+Control group in Study V72P16 received MenC conjugate with routine vaccines (InfanrixHexa, Prevenar) at 2, 3 and 4 months of age. At 12 months of age, these subjects received the first of two doses of rMenB+OMV NZ. Following the first dose, hSBA GMT against strain M10713 was 2.94 (95% CI: 2.26-3.82), N=93.
^Persistence of bactericidal activity was evaluated by comparing to the baseline of a newly recruited control group, which consisted of vaccine-naive subjects approx. 24 months of age. At baseline, hSBA GMT against strain M10713 was 2.32 (95% CI: 1.89-2.85), N=109.

Concomitant vaccinations:

The effect of concomitant routine infant vaccinations on rMenB+OMV vaccine was studied in V72P12, and the impact on routine infant vaccinations of concomitant vaccination with rMenB+OMV was studied in V72P12 and V72P1**3**. In study V72P13E1 rMenB+OMV was given with or without concomitant MMR vaccination.

Non-inferiority of responses to concomitantly administered routine infant vaccines was demonstrated for most antigens in studies V72P12 and V72P13. Non-inferiority of the immune responses to rMenB+OMV when given with or without routine infant vaccinations was only studied in V72P12. In this study non-inferiority was demonstrated for two of the antigens, fHbp (H44/76) and NadA (5/99), but not for the OMV (NZ98/254) or the NHBA (287-953) antigens. In the phase III study V72P13 the

rMenB+OMV vaccine was given concomitantly with the infant routine vaccinations, but no control group receiving the rMenB+OMV vaccine only was included. Thus, the responses to the vaccine are to some extent lower when the rMenB+OMV vaccine is given together with the routinely given infant vaccines, but the clinical relevance of the lower response is currently unclear. The responses to the rMenB+OMV vaccine in study V72P13 are considered robust (see above).

The response to MMRV vaccinations when given with or without rMenB+OMV vaccine was studied in V72P13E1. The non-inferiority criterion was achieved for the vaccine antigens Measles, Mumps and Rubella at the specified cut-off levels of ≥255 mIU/mL, ≥10 U/mL and ≥10 IU/mL, respectively. For Varicella, the non-inferiority was demonstrated for the cut-off level of ≥1.25 gpELISA units/mL (seroconversion) but could not be demonstrated for the higher cut-off level of ≥5 gp ELISA units/mL (seroprotection). The immune response was measured after the first dose of the licensed 2 dose series for the MMRV vaccine used in the study (Priorix-Tetra).

The effect of paracetamol on immune responses in infants

Preliminary data from study V72P16 demonstrated that the prophylactic use of paracetamol did not affect the immunogenicity of either Bexsero or routine vaccines. This study is included in the RMP, and a final report is awaited.

In addition, a post-hoc analysis of Study V72P13 data was performed evaluating the impact of antipyretic use on the bactericidal responses to three doses of rMenB+OMV NZ vaccine given at 2, 4 and 6 months of age. No significant differences were observed between subjects receiving antipyretics or not. In conclusion, paracetamol does not appear to decrease the immune responses to Bexsero in infants, when given prophylactic or therapeutically.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical studies include infants from 2 months, catch-up vaccination in 6-8 month and 12 month booster or primary vaccination, children 2-4 years, adolescents 11-17 years of age, and to some extent adults 18-50 years of age. Group B meningococcal disease mainly affects young children, with a second incidence peak in adolescents, and the use of the vaccine will mainly aim at protecting these age groups. However, in an outbreak situation, it may be desirable to be able to vaccinate the entire population in order to limit an epidemic. No data on immunosuppressed individuals, premature infants, and elderly are available.

There are no licensed commercially available vaccines against meningococcal group B disease which excludes the use of comparator vaccine to compare immunogenicity. In some studies a formulation of Bexsero without outer membrane vesicles (OMV) was used as a parallel group, in one study placebo was used as a control, and for safety a MenC conjugated vaccine was used as a control in the pivotal study V72P13.

In general the compliance was very good with few drop-outs. In the extension study V72P13E1 the number of groups was large. The different groups in V72P13E1 had been exposed to various background vaccinations from the main study V72P13 and for some of the populations analysed the number of excluded subjects was high (per protocol, persistence population).

Bactericidal assay as surrogate marker of protection

No efficacy studies have been performed in the clinical development of Bexsero. Efficacy studies against group B meningococci are not considered feasible due to the relatively low incidence of disease. The real benefit of Bexsero given to infants in a situation where circulating strains are heterogeneous, can only be evaluated after introducing the vaccine in a childhood vaccination program.

The strategy for demonstrating protection has aimed at determination of protective antibody responses against the four antigenic components of the vaccine, fHbp (936-741), NadA (961c), NHBA (287-953), and PorA1.4 (OMV NZ).

The bactericidal assay has been shown to correlate to protection against meningococcal disease in several studies. The cut-off established as a serological correlate of protection for group A, C W and Y meningococci is an hSBA titre ≥1:4, which has been used in studies aiming at regulatory approval of polysaccharide conjugate vaccines. The same cut-off has been used for group B meningococci, using a bactericidal assay, although the antigens used in the vaccine are not polysaccharides. The use of hSBA titre ≥1:4 has internationally been recognised as a correlate of protection against meningococci, including serogroup B. In addition, this cut-off has been shown to correlate to protection using OMV vaccines against serogroup B meningococci in Norway, Cuba and New Zealand. Considering that no efficacy data are available for this vaccine, it is not considered sufficient to base the evaluation of vaccine efficacy on a single threshold, but robust responses should be provided, e.g. higher threshold values and reverse cumulative distribution curves. It is possible that higher titres are required for long-term protection, and in at least some studies results have been presented also for SBA titres ≥1:8. Reverse cumulative distribution curves of SBA titres across studies were also submitted.

Taken together the SBA is considered a relevant method for demonstrating protective immune responses following vaccination with rMenB+OMV. The Company has requested CHMP Scientific advice regarding this issue several times during the development, and the CHMP has supported the overall strategy for demonstrating adequate immune responses.

In all studies SBA using strains specific for fHbp (936-741), NadA (961c), and PorA1.4 (OMV NZ) were used. For NHBA (287-953), a SBA strain (M10713) was recently established, and some data were provided in the initial application and in response questions during the assessment period. In some studies results from SBA using additional strains were also presented, i.e. V72P6, V72P9, V72P13, V72P6E1, V72P9E1 and V72P16.

Estimation of vaccine coverage

In order to estimate the overall protective efficacy against all MenB strains, a method for characterisation of strains regarding expression of the vaccine antigens in sufficient levels for susceptibility to bactericidal activity has been developed, termed “Meningococcal Antigen Typing System” or MATS. Whether a specific strain is killed by the vaccine induced immune response would depend both on immunological cross-reactivity and the level of the antigen expression in the target strain. MATS relative potency (RP) values reflect both parameters and were correlated with bactericidal activity against the 3 reference strains H44/76, 5/99 and NZ98/254, to establish bactericidal threshold values. MATS test values above the threshold means that a majority of tested serogroup B strains are killed in SBA.

When clinical isolates were used in the SBA instead of the reference strains, variable results were achieved and these were not always explained by the absence or presence of the main vaccine antigens (fHbp, NHBA, NadA, PorA). Another concern is the strict specificity and rapid decline of bactericidal antibodies against porA (OMV) and the low coverage provided by fHbp due to limited

cross-reactivity against other subvariants than the one in the vaccine and the low prevalence of the NadA antigen in Europe. All strains with the variant 1 of the fHBP will give a positive score in the MATS test, whereas it is evident from the clinical trials (V72P6, V72P9) that infants show a very limited cross-reactivity against other subvariants than the 1.1 present in the vaccine. The influence of sequence variability (subvariants) among fHBP variant 1 on bactericidal antibody responses has recently been published.

A group B meningococcal strain collection consisting of 1053 invasive clinical isolates from Norway, UK, Germany, France, and Italy collected during 2007-2008 has been established. The complete strain panel has now been characterised and based on MATS data derived from the 1052 typeable strains, an estimated 78% (95% CI: 63%; 90%) of strains are predicted to be covered by the vaccine. The available strain collection is likely to be representative of the situation in Western Europe. Data from Central and Eastern European countries will be collected in collaboration with ECDC.

Efficacy data and additional analyses

Infants: In the pivotal study (V72P13) immune responses were measured following three doses given at 2, 4 and 6 months of age. The primary endpoint was percentage of subjects obtaining an hSBA ≥1:5. Robust immune responses were demonstrated after three doses, 100% obtained SBA titres ≥1:5 against strains H44/76 and 5/99, and 84% against strain NZ98/254. These results are supported by the phase II study V72P12. Similar responses to strains H44/76, 5/99 and NZ98/254 were demonstrated after a priming schedule of 2, 3, 4 months.

Immunogical memory

In studies V72P13E1 and V72P6 the responses to a single booster does at 12 months of age were clearly stronger than the response to a single dose given to unprimed children, supporting that three doses given 2 months apart are sufficient to elicit immunological memory in infants. The immune responses up to 12 months after the 4th dose were studied in V72P13E2. The responses to fHbp and NadA were still high, while the responses to NHBA and OMV had decreased to lower levels.

Dose schedule

In study V72P12, rMenB+OMV was given at 2, 4 and 6 months of age or at 2, 3 and 4 months of age. The two schedules resulted in similar response rates in terms of hSBA ≥1:4 to fHbp, NadA and PorA, but the GMTs were slightly lower for the 2, 3, 4 months schedule. The responses to NHBA were considerably lower following the 2, 3, 4, month schedule. The Applicant is asked to describe plans for clinical studies of 2-dose priming in infants.

Catch-up vaccinations at 6-23 months: Immune responses to two doses at 6 and 8 months followed by a third dose at 12 months were studied in V72P9. The responses to the two-dose catch-up vaccination followed by a single dose at 12 months were adequate, as this schedule resulted in immune responses that were similar or higher than the 3+1 infant schedule.

In V72P13E1 two catch-up doses given at 12 and 14 or 13 and 15 months of age resulted in high immune responses, comparable to the responses seen following a single booster dose in previously primed infants. However, the immune responses to 2 doses waned over 12 months to NHBA and PorA suggesting the need for a third booster dose. TThe suggested posology for children 6 to 11 months of age should be 2 priming doses at least two months apart and one booster dose in the second year of life with an interval of at least 2 months between the primary series and the booster dose, whilst the suggested posology for children 12 to 23 months of age should be 2 priming doses at least two months apart and one booster dose to be administered with an interval of 12 months to 23 months between the primary series and booster dose

Children 2-11 years of age: Data on children 24-26 and 40-44 months of age demonstrate robust immune responses to the fHbp, NadA, PorA1.4 antigens, and slightly lower responses to NHBA. The responses are considered to be in agreement with results from younger and older subjects.

Adolescents: The immune responses in adolescents 11-17 years were studied in V72P10 only. This study was conducted in Chile. No data on vaccine antigen expression in circulating strains are available from Chile. The proportion of subject with baseline titres ≥1:4 against fHbp, NadA and PorA was similar in the Chilean study compared to adult studies in Europe (V72P4 and V72P5), supporting comparability of the study populations. A single dose of rMenB+OMV resulted in overall lower response rates compared to the 2- and 3-dose regimens. The difference in SBA response frequency between the 2- and 3- dose groups were very small, if any, which supports the recommended 2-dose schedule in adolescents. Thus, at least two doses are required to induce a strong response in this population. Antibody persistence was demonstrated up to 6 months following primary vaccination in adolescents, and booster responses to a single booster dose given 4-6 months following primary vaccination were demonstrated.

High levels of pre-existing antibodies to NHBA were demonstrated in V72P10. A number of reasons for this were presented, but no firm conclusions can be drawn. Titer increases were demonstrated following vaccination in subjects with pre-existing titres, as well as in subjects with titres below 1:4, indicating that Bexsero provides protection against strains expressing NHBA also in this age group.

Adults: Only limited data are available in adults. The study populations consisted of healthy adults 18-40 and 18-50 years of age respectively. No data are available in risk groups, or elderly. The immune responses were high after 2 doses, with IgG increases also after the 3rd dose. A decline of immune responses up to 6 months following vaccination was seen. No evidence of immunological memory or antibody persistence beyond 6 months is available. The suggested 2-dose schedule needs to be confirmed by follow-up data.

2.5.4. Conclusions on the clinical efficacy

Robust primary SBA responses against fHbp (936-741), NadA (961c), and PorA1.4 (OMV NZ) have been demonstrated in the relevant age groups. Overall, the responses to the NHBA antigen were lower than to the other antigens in terms of number of subjects with titres above 1:5. This was particularly concerning for infants given the 2, 3, 4 month schedule, and for the catch-up schedule in children over 12 months of age. The need for further booster doses is currently unclear, and the persistence of protective levels of antibodies is unknown.

2.6. Clinical safety

Eight studies were included to support the safety and tolerability of this vaccine, comprising 3 studies (V72P4, V72P5 and V72P10) in subjects 11 years of age and older (adolescents 11 to 17 years of age and adults 18 to 50 years of age) and 5 studies (V72P6, V72P9, V72P12, V72P13, and V72P13E1) in the infant and toddler populations (from 2 months of age). Five separate dosing regimens given to different age groups are discussed throughout, specifically:

1)
1) A 3-dose schedule administered at least 1 month apart for infants beginning from 2 months of age, followed by a booster in the second year of life
2) A 2-dose schedule administered 2 months apart for vaccine naïve older infants 6 months to 11 months of age, followed by a booster dose in the second year of life with an interval of at least 2 months between the primary series and booster dose

3) A 2-dose schedule administered 2 months apart for vaccine naïve children, 12 months to 23 months of age, followed by a booster dose with an interval of 12 months to 23 months between the primary series and booster dose
4) A 2-dose schedule administered at least 2 months apart in children 2 years to 10 years
5) A 2-dose schedule administered at least 1 month apart for adolescents and adults 11 years of age and older

Complete safety data are presented for all studies except study V72P10 in adolescents. Longer term safety follow-up of the study V72P10 is currently ongoing; the current submission includes only the unsolicited AE data from between day 1 and one month after the third vaccination at visit 4 (study month 3).

Patient exposure

The total number of subjects exposed to at least one dose of the rMenB+OMV NZ vaccine was 6427 subjects (from 2 months of age), including 4843 infants and toddlers with dosing regimen beginning from 2 to 12 months of age,1503 adolescents (11 to 17 years of age), and 81 adults (18 to 50 years of age). Of the subjects who received primary infant series of rMenB+OMV NZ, 1630 received a booster dose in the second year of life.

The pooled clinical safety database used to characterize the rMenB+OMV NZ safety profile includes 1503 adolescents 11 to 17 years of age, 81 adults 18 to 50 years of age and 4846 infant and toddlers with dosing regimen beginning from 2 to 12 months of age.

During the procedure, additional data for the following studies V72P16, V72P10, V72P6E1, V72P9E1, V72P12E1 and V72P13E2 were submitted. The Applicant should provide final study reports for studies V72P16 and V72P12E1, along with an updated summary of safety including all the above mentioned studies one month after Commission Decision.

Table 31 rMenB+OMV NZ Safety Populations

Study	Age at Enrollment	Number of Subjects		
		rMenB+OMV NZ	Comparators	Concomitant routine vaccine
V72P4	18-50 yrs	53	-	-
V72P5	18-40 yrs	28	-	-
V72P10	11-17 yrs	1503	128 (placebo)	-
Total		**1584**	**128**	
V72P6	2 months 12 months	50 24	49 (routine) -	DTaP-Hib-IPV, PCV7, MenC -
V72P12	2 months	1570[a]	312 (routine)	Infanrix Hexa and Prevenar
V72P13	2 months	2480[b]	659(routine) 490 (MenC)	Infanrix Hexa and Prevenar
V72P9	6-8 months	30	-	-
V72P13E1	12 months 12-13 months	291 401	- -	Subset with MMRV
Total		**4846**	**1510**	

[a]625 and 627 subjects with a 2,4,6 schedule with and without concomitant routine vaccinations and 318 with a 2, 3, 4 schedule with concomitant vaccinations;
[b]2, 4, 6 schedule with concomitant routine vaccinations; Note: DTaP-Hib-IPV= Pediacel, diphtheria, tetanus, acellular pertussis, poliovirus types 1, 2, 3, H. influenzae type b combined vaccine; PCV7 = Prevenar, heptavalent pneumococcal conjugate vaccine; MenC = Menjugate, meningococcal serogroup C conjugate vaccine

The safety follow-up period was at least 6 months. Overall 1630 subjects received a rMenB+OMV NZ booster dose in the second year of life and had a 6-month safety follow up period.

Table 32 Overview of Clinical Studies Included to Support rMenB+OMV NZ Safety (Booster Immunization)

Study number (Phase)	Age at enrolment	Schedule	Number in the safety population		Concomitant Routine vaccines
			rMenB-OMV NZ	Control	
V72P6 (Phase 2)	12 months	Booster at 12 months of age with 6-months safety follow-up	48[a]	None	Menitorix
V72P9 (Phase 2)		Booster at 12 months of age with 6-months safety follow-up	27b	None	None
V72P13E1 (Phase 3)		Booster at 12 months of age with 6-months safety follow-up	1555	None	Priorix-Tetra
Total			1630	0	

[a]48 of the 50 subjects received the fourth (booster) dose; [b]27 of the 30 subjects received the third dose (booster).

Overview of Adverse events

Adolescents and Adults

11 to 17 Years of Age

From study day 1 and month 4, the most commonly reported unsolicited AEs after any vaccination was nasopharyngitis (range, 6% to 8%) including placebo. The most common AE that was possibly or probably related after any vaccination was injection site pain. Between study day 1 and month 3, the most frequently reported unsolicited AEs were similar for the two-dose schedule, regardless of dosing interval: nasopharyngitis, headache, injection site pain, induration, and swelling, and pharyngitis were reported in at least 2% of subjects. No other individual AE by preferred term was reported by more than 2% in any of the two-dose schedule groups.

Within 30 days of vaccination, the most frequently reported unsolicited AEs were similar for the rMenB+OMV NZ and placebo vaccine groups: nasopharyngitis, injection site pain, and bronchitis were reported by no more than 4% of subjects in at least one of the vaccine groups; no other individual AE by preferred term was reported by more than 2% of the subjects in any vaccine group

Overall, the percentage of subjects reporting AEs was lower with additional vaccination and similar across dose groups. Most of the AEs after each vaccination were mild and few were moderate. Severe AEs were infrequently reported across the vaccine groups. The percentage of subjects reporting AEs after each vaccination was similar between the groups receiving two or three doses, respectively of the rMenB+OMV NZ vaccine. The most commonly reported possibly related unsolicited AEs were local reactions continuing past the 7-day observational period: injection site pain and induration were reported similarly across dose groups.

18 to 50 Years of Age

Between study day 1 and month 3 after vaccination, the most frequently reported unsolicited AEs were lower in the adult subjects than the adolescent subjects with a similar dose schedule: nasopharyngitis, pharyngitis, and injection site pain and indurations were reported by 1% to 7% of the subjects. No other individual AE by preferred term was reported by more than 2% in any of the two-dose schedules. A lower percentage of adult subjects reported events that were judged by the investigator to be possibly or probably related AEs than for the adolescent subjects with similar dose schedule (0-1-month schedule: 4% vs. 17% and 0-2-month schedule: 13% vs. 16%, respectively. The most commonly reported possibly or probably related unsolicited AEs were local reactions ongoing past the 7-dayobservational period: swelling and injection site pain and injection site induration.

Infants and Toddlers

Infants

Overall, between study day 1 and 7 months of age, the most commonly reported AEs after any vaccination with rMenB+OMV NZ with concomitant routine vaccines at the 2, 4, 6- month schedule were *injection site induration* (42%), *erythema* (13%), and *swelling* (9%; mostly considered as possibly related to vaccination as these local reactions of *induration, erythema,* and were solicited AEs continuing after the 7-day vaccination window and *upper respiratory tract infections* (10%); mostly considered unrelated to vaccination. Injection site AEs were more frequently reported in subjects receiving rMenB+OMV NZ with concomitant routine vaccines than those receiving MenC with concomitant routine vaccines or routine vaccines only.

Older Vaccine Naive Infants and Toddlers (2-dose schedule)

In the older vaccine naive infants subjects who received a 2-dose primary series of rMenB+OMV NZ vaccine at 6 to 8 months of age, the most frequently experienced unsolicited AEs were *teething* (27%), *cough* (20%), and *conjunctivitis* (17%).; The most frequently experienced possibly or probably related unsolicited AEs were *erythema* (13%), *induration* (13%), and *cough* (10%). The most commonly reported AE by preferred term in vaccine naive toddlers was *injection site induration* which was reported by between 24% and .33% of subjects who received a 2-dose primary series vaccination at 12 or 13 months of age.

Booster Dose in Toddlers (at 12 months of age)

The most commonly reported AE by preferred term was "*injection site induration*" which was reported by 21% who received a 12-month booster administered with or without concomitant Priorix-Tetra vaccine. The most frequently experienced unsolicited AEs in older, vaccine naive infants who received a third (booster) dose of the rMenB+OMV NZ vaccine at 12 months of age were *teething, rhinitis*, and *cough* .The most frequently experienced possibly or probably related unsolicited AE was *rhinitis.*

Table 33 Overview of Unsolicited AEs in Infants

	Percentages of Subjects							
	Primary Period							
	2,4,6 Schedule						2,3,4 Schedule	
Group V72 Studies	MenB+R Total P6+P12+P13	MenB+R P13	MenC+R P13	Routine P13	MenB+R P12	MenB+R3,5,7 P12	MenB+R P12	Routine P12
	N=3155	N=2480	N=488	N=658	N=625	N=627	N=318	N=312
Any AEs	2431 (77)	1924(78)	309 (63)	468 (71)	462(74)	531 (85)	211 (66)	195 (63)
At least possibly related AEs	1642 (52)	1339 (53)	204 (42)	226 (34)	290(46%)	336 (54)	145 (46)	96 (31)
Serious AEs	128 (4)	90 (4)	13 (3)	17 (3)	37(6)	35 (6)	5 (2)	10 (3)
	Follow-up Period							
Any AEs	1690 (54)	1336 (54)	172 (35)	366 (56)	347 (56)	321 (51)	174 (55)	167 (54)
At least possibly related AEs	9 (<1)	7 (<1)	1 (<1)	2 (<1)	2 (<1)	2 (<1)	2 (1)	1 (<1)
Serious AEs	156 (5)	125 (5)	15 (3)	35 (5)	28 (4)	26 (4)	15 (5)	10 (3)

R=Routine

Serious adverse event / deaths

There were no deaths reported in any of the studies.

Across all ages, reports of SAEs were infrequent both for the rMenB+OMV NZ and comparator groups within each study and in most part classified under the system organ classes (SOCs) “infections or infestations” and “general disorders and administration site conditions” Overall, no increased risk of any specific SAE considered to be clinically significant in infants, toddlers, adolescents and adults vaccinated with rMenB+OMV NZ was identified upon review of the SAEs across studies.

Adolescents and Adults

11 to 17 Years of Age

Ten subjects reported AEs that were assessed to be serious. All of the subjects recovered within the observation period.

The majority of SAEs were adverse events coded to SOC “infections or infestations” and most of these were moderate in severity

18 to 50 Years One

One subject in the study V72P5 in rMenB+OMV NZ group was diagnosed with *HIV infection.* This SAE was assessed as not related to study vaccination.

No SAEs were reported for study V72P4.

Infants and Toddlers

A total of 52 subjects in the infant and toddler population experienced SAEs that were clinically significant and 19 events were considered possibly or probably related by the investigator.

Throughout the studies, SAEs were infrequently reported as no more than 1% of infants reported SAEs after the first, second, and third dose.

The SOCs most affected were “infections and infestations” and “general disorders and administration site condition” across the three doses administered (<1%).

The SOCs most affected were “infections and infestations” and “general disorders and administration site condition” across the three doses administered (<1%).

Adverse Events of Special Interest

Fever

The safety profile of rMenB+OMV NZ in the second year of life comes mainly from study V72P13E1 in which subjects from study V72P13 received either a fourth booster dose at 12 months of age or 2-doses 2-months apart in immunologically naive toddlers at either 12, 14 or 13, 15 months with and without concomitant administration of the MMRV (i.e., measles, mumps rubella and varicella) live-attenuated combination vaccine (Priorix Tetra). Local and systemic reactions were collected for days 1-7 after rMenB+OMV NZ vaccination and for days 1-28 after MMRV vaccination.

Fever (≥38.0°C) was reported for 41% to 58% of subjects (across groups) and no more than 1% (4 for 12B12M, N=765; 2 for 12B13M, N=789) of subjects had fever ≥40°C. Overall fever rates of rMenB+OMV NZ were comparable to that of the Priorix Tetra vaccine. Moreover, the fever associated with rMenB+OMV NZ vaccination was predictable, occurring early after vaccination, and transient, with the majority resolving within 2 days. Fever ≥38°C within 7 days of vaccination was reported more when concomitantly administered with the Priorix Tetra than when rMenB+OMV NZ was given alone (46% vs. 37%), A more detailed analysis of fever was performed by comparing the daily fever rates for the month (days 1-28) after the 12 months of age vaccination in groups rMenB+OMV NZ alone (12B13M g.) Fever was mostly reported during the 1-4 days after the rMenB+OMV NZ vaccination alone and during the 5-28 days after the Priorix Tetra vaccination alone. When rMenB+OMV NZ was given concomitantly with the Priorix Tetra vaccine, the fever rates showed a trend towards an additive rather than a synergistic effect of the two vaccinations i.e. fever reported during the 1-3 day period as well as during the 5-28 day period after the vaccinations. The rate and magnitude of fever were similar between rMenB+OMV NZ and Priorix Tetra (MMRV) vaccine.

Study V72P16 evaluated the effect of administering paracetamol as prophylaxis against fever caused by vaccination. When paracetamol was given just before vaccination (Bexsero + routine vaccines), followed by two doses 4-6 hours apart, the rate of fever decreases significantly. The fraction of subjects with fever ≥ 38.5°C decreases from 69% in non-treated group to 39% in the group receiving paracetamol. Thus, it was suggested that the fever associated with Bexsero can be managed by using antipyretics, or by other means such as separating routine vaccination from vaccination with Bexsero and by proper information to parents.

In the rMenB + OMV NZ group that did not receive prophylactic paracetamol. 56%, 55%, 36% and 54% of subjects were treated at least once during the 7 days after the first, second, third and fourth dose of rMenB + OMV NZ respectively which shows that there is a high fever rate after vaccination.

Table 34 Numbers (%) of Subjects Reporting Antipyretic Medication Use by rMenB+OMV NZ Dose in the Non-Prophylactic Control Arm of Study V72P16

	rMenB+OMV NZ 2, 3, 4-Month Schedule Non-Prophylactic Paracetamol Treatment Group
Dose	
1	56% (102/182)
2	55% (100/182)
3	36% (66/181)
4	54% (84/155)

Seizures

In the pivotal studies V72P12 and V72P13 representing ~4000 subjects exposed to Bexsero. 3 cases of febrile seizures were reported within 2 days of vaccination. In 2 cases Bexsero were co- administered with Infanrix hexa and Prevenar and in one case Bexsero was given alone. One of the subjects had a pre-existing neurological condition. Fever associated with vaccination occur typically within 2 days after vaccination with an onset around 6 hours post vaccination

Non-febrile seizures were reported in nine subjects by onset interval from the last dose of study vaccine. Two cases of convulsions occurred on the same day as the vaccinations with rMenB+OMV NZ, InfanrixHexa and Prevenar and were judged by the investigators as possibly related to the study vaccinations. These events were reported as transient, non-serious adverse events of mild or moderate severity. The remaining seven subjects, five of whom were in the rMenB+OMV NZ group and two in the control group, all experienced seizures after the third study vaccinations. The episodes occurred anywhere from 1½ to 6 months after the vaccination dose.

In summary, although definitive conclusions based on these observations cannot be made due to the relatively small number of cases, the foregoing analysis provide no evidence of an increased risk of febrile or non-febrile seizures associated with administration of Bexsero in small children.

Kawasaki Disease

There were 7 cases of suspected Kawasaki Disease (KD) reported in phase 2 and phase 3 clinical studies with rMenB+OMV NZ (2 cases in study V72P12, 4 cases in study V72P13 and 1 case in the extension study V7213E1. Six cases were in recipients of the rMenB+OMV NZ and one in a control subject receiving Men C conjugate. There was no significant difference in KD (confirmed or likely) incidence rates between the rMenB+OMV NZ and control groups and the KD cases were not clustered within a timeframe consistent with a causal relationship between rMenB+OMV NZ vaccination and KD. Overall, these few KD cases do not allow a definitive assessment of the causal relationship between rMenB+OMV NZ vaccination and the disease also considering the co-administration of rMenB+OMV NZ with other vaccines is a confounding factor in many of the cases.

HHE

Two hypotonic-hyporesponsive episode (HHE) cases (one within 1 day of vaccination with rMenB+OMV NZ co-administered with Infanrix Hexa and Prevenar and the other event on the same day of vaccination with the routine vaccines) were observed in studies V72P12 and V72P13 These rates are within the expected range and provide evidence against an increased risk of HHE associated with rMenB+OMV NZ vaccination.

Overall, these AEs of special interest either occurred at an expected frequency for the relevant age or a causal relationship between rMenB+OMV NZ vaccination and the occurrence of the event could not be clearly established.

No AEs leading to withdrawal and no other significant AEs raised a safety concern.

Laboratory findings

Two abnormal laboratory values in subjects receiving rMenB+OMV NZ were assessed as clinically significant (one case of elevated γGT value (131 U/L), and one positive HIV test and were described in study V72P5.

Immunological events

No immunological events except for few cases of urticaria and rash were recorded or described in the provided study safety data.

No autoimmune disorders were described.

Safety related to drug-drug interactions and other interactions

The clinical studies included concomitant administration of other vaccines such as Infanrix Hexa, Prevenar and Priorix Tetra (MMRV). The safety data are presented with the assessment of study reports.

Discontinuation due to adverse events

Discontinuations were reported from adult study V72P4 where two subjects were withdrawn, one due to syncope day 1 and another due to nasopharyngitis on day 212. Additionally one subject was confirmed with pregnancy and withdrew her consent. In adolescent study V72P10 one subject withdrew due to convulsions two minutes after the first vaccination. No withdrawals with possible relationship to vaccinations were described from the infant and toddler studies.

2.6.1. Discussion on clinical safety

Overall, the data presented indicate that rMenB+OMV NZ has an acceptable safety profile based on a controlled safety database of 4846 infants and toddlers and 1584 adolescents and adults receiving at least one dose of rMenB+OMV NZ in clinical studies used to support the vaccine safety claims in this application. The database is sufficient to detect adverse reactions in the frequency 1/1000, but an extended database would be required to identify more unusual adverse events. The Applicant has included post-authorisation studies in the Pharmacovigilance Plan with the aim of increasing the safety database and continuing to characterise the safety profile of Bexsero.

The use of rMenB+OMV NZ in infants was associated with frequent reports of reactogenicity and especially of local reactions. Most of these were of mild or moderate severity and transient. Reactogenicity overall was higher after administration of vaccine including OMV. Co-administration of rMenB+OMV NZ+ Priorix Tetra was more reactogenic than any of the vaccines alone.

rMenB+OMV NZ vaccination in the infant population was associated with increased rates of fever, which is consistent with safety data collected after administration of other OMV based vaccines. Generally the recipients of rMenB+OMV NZ vaccine experienced higher rates of fever compared with those receiving Men C vaccine with routine vaccines or the routine vaccines alone. Fever associated

with rMenB+OMV NZ + routine group and with onset mainly occurred between 6 hours and one day post-vaccination. The majority of fever resolved within 48 hours. Medically attended fever in the rMenB+OMV NZ + routine and comparator groups occurred with a frequency of <1% to 3% of subjects across vaccine groups. The higher rates of fever were not associated with an increase in medically attended events. In all presented clinical studies, antipyretics were given after vaccination. Preliminary reactogenicity data from an ongoing study using a 2, 3, 4 vaccination schedule suggest that use of paracetamol just before vaccination may reduce fever rates by approximately 50% after the first dose. Analgesics/antipyretics medications were frequently used and, consistent with the higher fever rates, more common in the rMenB+OMV NZ + routine group than for MenC +routine and routine alone. Therapeutic antipyretic treatment was more common than prophylactic antipyretic treatment.

Although the accelerated 2, 3, 4 schedule given with routine vaccinations was used in a relatively small (N= 318) proportion of the infant safety population, it was considered that this number was sufficient to detect common adverse events, such as fever. As the safety profile of rMenB+OMV NZ was most comparable to that of rMenB+OMV NZ given at 2, 4, 6 months of age with concomitant routine vaccines, these data would most likely support the use of the vaccine with either schedule.

No immunological reactions – except for urticaria and rash – or autoimmune disorders have been noted in the safety reporting.

Adverse events of special interest observed are convulsions – with or without fever, HHE and Kawasaki disease which are all labelled in section 4.8 of the SPC.Regarding the seven reported KD cases these do not allow a definitive assessment of the causal relationship between rMenB+OMV NZ vaccination and the co-administration of rMenB+OMV NZ with other vaccines is a confounding factor in many of the cases. Geographical and temporal clustering was observed and as well as a seasonal variation of the cases which together with a wide range of onset intervals for the cases following vaccination may question a causal relation between rMenB+OMV NZ vaccination and KD. The actual cause of Kawasaki disease is not completely known. It has been suggested that the disease, with symptoms of vasculitis may be autoimmune but some infectious origin has also been discussed. The disease often appears in clusters and during spring or in autumn in mostly children aged less than 5 years. Kawasaki disease will be investigated in a post-licensure observational study and is included as a potential risk in the RMP.

2.6.2. Conclusions on the clinical safety

The safety data base is considered to be sufficient to detect adverse reactions in at least a frequency of 1:1000 and appropriate as safety data package for licensure. The provided safety data show that the reaction patterns regarding local as well as systemic reactions were similar within all studies in the different age cohorts.

Overall, the safety profile is comparable with what would be expected after vaccination with any of the routine vaccines administered in the related age-groups. Generally, no significant differences in the frequency of AEs after incremental dose occurred. The intensity of the adverse events did not increase by dose. Co-administration with rMenB+OMV NZ and Priorix Tetra showed increased reactogenicity compared to the other vaccines – co-administered or alone.

The applicant agreed to investigate potential risks such as febrile seizures and Kawasaki Disease in a post-licensure observational safety study as part of the pharmacovigilance activities.

Study V72P16 evaluated the effect of paracetamol as prophylaxis against fever caused by vaccination. Study results suggested that the fever associated with Bexsero can be managed by using antipyretics,

or separating routine vaccination from vaccination with Bexsero. This information has been introduced in the relevant sections of the Product Information.

Additional to the post-authorisation studies proposed by the Applicant, the CHMP considers the following measure necessary to address any potential issues related to safety:

An updated integrated safety summary including studies V72P16 and V72P12E1 should be submitted one month after Commission Decision.

2.7. 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 applicant submitted a risk management plan version 4 of 12 November 2012.

Summary of the risk management plan

Safety concern	**Proposed pharmacovigilance activities (routine and additional)**	**Proposed risk minimization activities (routine and additional)**
Important identified Risk:		
Fever	Routine PV V72P16 study and paracetamol	Routine minimization with SmPC and package leaflet for the management of the fever: 4.4 Special warnings and precautions for use: “As with many vaccines, health care professional should be aware that a temperature elevation may occur following vaccination of infants and children (less than 2 years of age). Prophylactic administration of antipyretics at the time and closely after vaccination can reduce the incidence and intensity of post-vaccination febrile reactions. Antipyretic medication should be initiated according to local guidelines in infants and children (less than 2 years of age).”
Important potential risks:		
Guillain-Barré Syndrome	Enhanced pharmacovigilance with questionnaire and adjudication by SMT and post-licensure observational safety surveillance study V72_36OB	None
Acute disseminated encephalomyeli	Enhanced pharmacovigilance with questionnaire and adjudication by SMT and post-	None

tis	licensure observational safety surveillance study V72_36OB	
Anaphylaxis and Anaphylactic Shock	Routine pharmacovigilance Post-licensure observational safety surveillance study V72_36OB	Routine minimization with SmPC or country specific equivalent labeling with section 4.3 contraindications: “Hypersensitivity to the active substances or to any of the excipients listed” and section 4.4 Special Warnings and Precautions:” As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine.”.
Chronic Fatigue Syndrome	Routine Pharmacovigilance	None
Kawasaki Disease	Enhanced pharmacovigilance with questionnaire and adjudication by expert panel and post-licensure observational safety surveillance study V72_36OB “Plan B” studies: V72_47OB	Routine minimization with SmPC section 4.8 and package leaflet: Undesirable effects:” Vascular disorders Rare: Kawasaki syndrome”
Seizure and febrile seizure	Enhanced pharmacovigilance with questionnaire and adjudication by SMT and post-licensure observational safety surveillance study V72_36OB “Plan B” studies: V72_47OB and V72_52OB V72P16 and V72P13E2 additional data	Routine minimization with SmPC section 4.8 and package leaflet: Undesirable effects:” Nervous system disorders, Uncommon: seizures (including febrile seizures)”
Decrease immunogenicity after prophylactic use of paracetamol	Routine pharmacovigilance V72P16 study and paracetamol	Routine minimization with SmPC section 4.5 and package leaflet: “Due to an increased risk of fever, tenderness at the injection site, change in eating habits and irritability when Bexsero was co-administered with the above vaccines, separate vaccinations can be considered when possible. Prophylactic use of paracetamol reduces the incidence and severity of fever without affecting the immunogenicity of either Bexsero or routine vaccines. The effect of antipyretics other than paracetamol on the immune response has not been studied.”
Important missing Information:		
Vaccine	Post-licensure observational vaccine effectiveness study	None

effectiveness	V72_38OB study "Plan B" studies: V72_48OB and V72_53OB	
Vaccine failure	Enhanced pharmacovigilance with SMT adjudication on pre-establish criteria and research every 6 months in the database V72_38OB study "Plan B" studies: V72_48OB and V72_53OB	None
Strain/serotype replacement	Nasopharyngeal Carriage study to define the next step.V72_29 study and V72_38OB study "Plan B" studies: V72_48OB and V72_53OB	None
Elderly	Routine pharmacovigilance	Routine minimization with SmPC section 4.4 and package leaflet: "There are no data on the use of Bexsero in subjects above 50 years of age".
Immuno-compromised subjects	Routine pharmacovigilance Study V72_31 in terminal complement component deficiency subject	Routine minimization with SmPC section 4.4 Special warnings and precautions for use
Chronic Medical Condition patients	Routine pharmacovigilance	None
Safety of vaccine during pregnancy	Post-licensure observational pregnancy study (V72_39OB) Alternative studies if vaccine uptake is low in planned study centers.	Routine minimization with SmPC section 4.6 and package leaflet: Pregnancy and breast-feeding. Insufficient clinical data on exposed pregnancies are available. The potential risk for pregnant humans is unknown. Nevertheless, vaccination should not be withheld when there is a clear risk of exposure to meningococcal infection. There was no evidence of maternal or foetal toxicity, and no effects on pregnancy, maternal behavior, female fertility, or postnatal development in a study in which female rabbits received Bexsero at approximately 10 times the human dose equivalent based on body weights."
Compliance in adolescent and	Routine pharmacovigilance V72P10 including the booster	Routine minimization with stickers for traceability of the 2 doses

young adult	dose	

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

Description	Due date
V72_29 nasopharyngeal carriage study to evaluate the effect of Bexsero and MenACWY Conjugate vaccines on Pharyngeal Carriage of N. meningitidis in young adults	Final CSR by 30 June 2012
V72_31 study in individuals with terminal complement component deficiency or functional or anatomic asplenia	Final CSR by 31 December 2016
Post-approval observational study assessing the safety of Bexsero vaccination in routine care. (V72_36OB) If vaccine uptake is slow in the country(ies) where the safety study is planned, alternative study sites will be identified ("Plan B" studies: V72_47OB and V72_52OB)	Interim reports every 6 months for first 2 years Annual interim reports until the end of the study, after the first 2 years Final CSR by 31 December 2017 Final CSR for "Plan B" studies by 31 December 2018
Post-approval observational study is to assess the impact on invasive meningococcal disease (all serogroups) and effectiveness of Bexsero vaccination against MenB and vaccine-type disease (V72_38OB) If vaccine uptake is slow in the country(ies) where the effectiveness study is planned, alternative study sites will be identified ("Plan B" studies: V72_48OB and V72_53OB)	Interim reports every 6 months for first 2 years Annual interim reports until the end of the study, after the first 2 years Final CSR by 31 December 2017 Final CSR for "Plan B" studies by 31 December 2018
Post-authorisation observational study for monitoring use of Bexsero in pregnancy (V72_39OB) If vaccine uptake is slow in the country(ies) where the observational study is planned, alternative study sites will be identified in the context of a National Immunization Program which includes an adolescent catch-up schedule.	Interim reports every 6 months for first 2 years Annual interim reports until the end of the study, after the first 2 years Final CSR by 31 December 2017
Safety analysis and summary as an update of eCTD module 2.7.4	Safety report due one month after Commission Decision
Study V72P16 (infants) and V72P12E1 (children)	Final CSR due one month after Commission Decision

No additional risk minimisation activities were required beyond those included in the product information.

In addition, the CHMP considered that the applicant should take the following minor points into consideration when an update of the Risk management Plan is submitted:

The RMP should include when possible update detailed plans for effectiveness and safety studies in the case of low uptake of vaccine in the countries where the current pharmacovigilance studies are

planned (“Plan B” studies). Study protocols should be submitted with the RMP update, for review of PRAC, together with criteria for triggering the start of the named studies.

2.8. Significance of paediatric studies

The CHMP is of the opinion that studies V72P6, V72P9, and V72P13, which are contained in the agreed Paediatric Investigation Plan (P/38/2011) and have been completed after 26 January 2007, are considered as significant.

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Bexsero is intended for vaccination against group B meningococci. In Europe serogroup B is the most prevalent meningococcal serogroup, with 3406-4819 cases being reported annually between 2003 and 2007 as per European Center of Disease Control surveillance report for 2007. Efficacy was estimated using a serological correlate of protection, serum bactericidal antibodies (SBA). This considered an acceptable approach. High rates of SBA responses have been demonstrated against all four vaccine components in infants and adolescents following 3 and 2 doses respectively. The SBA titer cut-off used in these studies (≥1:4 or 1:5) is considered an acceptable correlate of protection. In addition, these results are supported by data on response rates using a higher cut-off, e.g. ≥1:8. Also in adults, immune responses to three of the vaccine components have been determined, although the study population was comparatively small.

The proposed amount of antigen in each dose has been demonstrated to be adequate based on interim data from the dose-finding study V72P16 in infants, as well as the previous experience with the OMV component alone.

Booster responses to all four antigens were shown at 12 months of age in infants previously vaccinated with 3 doses at least 1 month apart starting at 2 months of age and infants receiving two doses starting at 6 months of age. Data in adolescents supported the presence of immunological memory at 6 months following primary vaccination.

Uncertainty in the knowledge about the beneficial effects

Although the immune responses measured by SBA are expected to be protective, no efficacy data are available. This does not preclude the granting of the marketing authorisation based on immunogenicity data. However vaccine effectiveness is required in the post-authorisation phase. The CHMP took into account the difficulties in obtaining such data pre-approval and the plans for post-marketing effectiveness studies after vaccine introduction were considered acceptable.

The duration of protection is currently unknown. In infants the antibody levels declined rapidly for the PorA and NHBA antigens, i.e. within 6 months of primary vaccination, and within 12 months of booster or primary vaccination in toddlers. The antibody titres in infants against fHbp were also shown to decline although not as much as the PorA titres. The proportion of subjects with SBA titres to fHbp ≥1:5 was 50-60% at 12 months after the fourth dose in V72P13E2.

Data was considered limited in adults and lacking in elderly and risk groups, such as immunosuppressed individuals. The applicant put in place pharmacovigilance activities to address the missing information which were considered acceptable by the CHMP.

The data obtained in adolescents were from a Chilean population, but considering that the pre-vaccination antibody levels to fHbp, NadA and PorA were similar in the Chilean adolescents as in European adults, the study results were considered relevant to a European population. The immune responses to NHBA in Chilean adults could not be directly compared to European adults, but a high proportion of both populations have antibodies to NHBA. The CHMP considered important to obtain data in European adolescents. Therefore, the applicant committed to conduct a study on nasopharyngeal carriage of *N. meningitidis* in young adults (V72_29) that would provide serological relevant for the use in adolescents.

Immunological memory has been demonstrated at 12 months of age following a 3-dose priming schedule in infants 2, 4, 6 or 2, 3, 4 months of age. Memory has not been demonstrated beyond this age group, after any other priming schedule or after a longer time period. Data on antibody persistence and immunological memory have not been presented beyond 6 months after the last dose.

The risk for strain replacement could be lower for a protein based meningococcal vaccine compared with the capsular polysaccharide vaccines, as capsular switching is unimportant in this case. The potential protective efficacy against other meningococcal strains is currently unknown, however will be addressed in the epidemiological surveillance to be conducted post-licensure.

Risks

Unfavourable effects

Injection site reactions were very common and are labelled in the SmPC. Fever ≥ 38ºC occurs commonly with rMenB and rMenB+OMV and more pronounced when co-administrated with routine vaccines than with these vaccines alone, i.e. 96% experienced fever after any dose of Bexsero + routine vaccines, versus 80% after any dose of routine vaccinations only.

The safety database is large enough to detect adverse reactions in the frequency of 1/1000 and considered adequate for the approval phase of a vaccine.

Some serious adverse events, e.g. convulsions/seizures – febrile and non-febrile and Kawasaki disease were reported in clinical studies. These potential risks will be monitored by enhanced pharmacovigilance and post-licensure observational safety studies will be conducted.

Uncertainty in the knowledge about the unfavourable effects

There is insufficient knowledge about immunological and/or autoimmune reactions after administration of rMenB and rMenB +OMV NZ or co-administered with routine vaccines. Data in elderly or immunosuppressed individuals is missing

Pharmacovigilance activities are in place to monitor missing information in these populations. In addition statements have been included in the relevant section of the Product Information.

Benefit-risk balance

Importance of favourable and unfavourable effects

There is currently no vaccine against group B meningococci licensed in the EU. A vaccine against the majority of group B meningococcal strains is considered valuable in areas with high incidence rates. It would also be valuable to have a vaccine available in an outbreak situation.

The demonstrated functional immune responses are considered highly relevant for an estimation of efficacy in the absence of efficacy data. The risks of fever (very common), seizures including febrile seizures (uncommon) and Kawasaki disease (rare) have been identified but found to be acceptable in situations of increased risk of meningococcal disease caused by group B meningococci.

The remaining limitations in knowledge regarding both benefit (vaccine effectiveness, duration of immunity) and risk (Kawasaki disease and other rare events), are addressed in the post-marketing activities. However, it is recognised that the feasibility and efficiency of these studies depend on extent of uptake of the vaccine.

Benefit-risk balance

There is a clear benefit of protection against group B meningococci in areas with high incidence of disease. Currently, the functional immune responses as measured with SBA indicate that robust immune responses are elicited. The available coverage data suggest that the vaccine will protect against the majority (78%) of circulating strains. The benefit is considered relatively small in the general EU population, as group B meningococcal disease is uncommon in Europe (3400-4800 cases annually). However, there are regions with higher incidence as well as large outbreaks that are difficult to control without access to an appropriate vaccine. In these cases the benefit of vaccination would be greater. The identified risks are considered small. Guidance to prescribers is provided in the event of increased risk of fever when used concomitantly with routine infant vaccine.

Discussion on the benefit-risk balance

The exact beneficial effect of Bexsero will not be possible to conclude until post-marketing efficacy studies are available. However, the presented data on functional immune responses indicate that vaccination with Bexsero will protect against invasive disease caused by group B meningococci. The proposed indication is considered approvable based on the available clinical and epidemiological data.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Bexsero for the following indication: “active immunisation of individuals from 2 months of age and older against invasive meningococcal disease caused by *Neisseria meningitidis* group B is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Official batch release

In accordance with Article 114 Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

Conditions and requirements of the Marketing Authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP shall be submitted annually until renewal.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

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

Not applicable

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

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that OMV, protein 961c, protein 287-953 and protein 936-741 contained in the medicinal product Bexsero are to be qualified as new active substances in themselves.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan (P/38/2011) and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In accordance with Article 45(3) of Regulation (EC) No 1901/2006, significant studies in the agreed paediatric investigation plan (P/38/2011) have been completed after the entry into force of that Regulation.