Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Multi-Component Meningococcal B vaccine

Proprietary Product Name: Bexsero

Sponsor: Novartis Vaccines and Diagnostics Pty Ltd

Date of first round CER: 24 April 2012
Date of supplementary CER: 3 May 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities. The original text has been modified only to remove lot numbers and to replace 'H44/76' with '44/76' in line with terminology used currently.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations and definitions

Abbreviation	Meaning
ADEM	Acute disseminating encephalomyelitis
BCA	Bactericidal Complement Assay
CER	Clinical Evaluation Report
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
LPS	Lipopolysaccharide
MATS	Meningococcal Antigen Typing System
MedDRA	Medical Dictionary for Regulatory Activities
MenB	Serogroup B meningococcus

Abbreviation	Meaning
MenBvac	Outer membrane vesicle vaccine derived from *Neisseria meningitidis* serogroup B strain 44/76. This vaccine was developed by the Norwegian Institute of Public Health in response to the outbreak of group B meninogococcal disease in that country starting in the 1970s. It has been referred to as H44/76 or 44/76-SL in some publications and clinical study reports. [Note: H44/76 is referred to as 44/76 in the approved Bexsero Product Information]
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 44/76 (Norwegian strain)
PCV7	PrevenarTM pneumococcal vaccine (7-valent pneumococcal conjugate vaccine)
PP	Per Protocol
RPT	Rabbit pyrogen test
SBA	Serum Bactericidal Assay
SOC	System Organ Class
WHO	World Health Organization

Vaccine antigens	
fHBP	factor H binding protein derived from MenB strain MC58, is included in the vaccine as a recombinant protein which is fused with accessory protein coded 936, derived from MenB strain 2996. The fHBP recombinant fusion protein has been previously referred to as 936-741 or GNA2091-1870.
NadA	Neisseria adhesin A (NadA). NadA is included in the vaccine as a single recombinant protein derived from MenB strain 2996. The NadA vaccine antigen is also referred to by the company code 961c.
NHBA	Neisserial Heparin Binding Antigen (NHBA) fusion protein. NHBA, derived from MenB strain NZ98/254, is included in the vaccine as recombinant protein which is fused with accessory protein coded 953, derived from MenB strain 2996. NHBA, as an individual recombinant protein, has also been referred to by the company code 287. The 287 and 953 recombinant protein antigens are also known in publications as GNA2132 and GNA1030, respectively (GNA [genome-derived neisserial antigen]). The NHBA recombinant fusion protein has been previously referred to as 287-953 or GNA2132-1030
PorA P1.4	PorA P1.4 is the immunodominant protein antigen contained in the outer membrane vesicle derived from MenB strain NZ98/254 (OMV NZ). PorA P1.4 is the main target for bactericidal antibodies generated after immunisation with OMV NZ.

Vaccine formulations	
rMenB+OMV NW	formulated with the three recombinant protein antigens (fHBP, NadA, NHBA)and OMV NW derived from *Neisseria meningitidis* Serogroup B strain H44/76 (Norwegian strain). Evaluated in studies V72P1, V72P2, V72P3 and V72P5
rMenB+OMV NZ	the final Phase 2b/3 vaccine formulation containing the three recombinant protein antigens (fHBP, NadA, and NHBA,) and OMV NZ derived from *Neisseria meningitidis* serogroup B strain NZ98/254 (New Zealand strain). Evaluated in studies V72P4, V72P5, V72P6, V72P9, V72P10, V72P12, V72P13, and V72P13E1
4CMenB	proposed generic name for rMenB+OMV NZ (4-component MenB)

1. Introduction

This submission is to register Bexsero for active immunisation against invasive disease caused by *N. meningitidis* serogroup B strains in individuals from 2 months of age and older.

Multi-component Meningococcal B vaccine (NadA, fHBP, NHBA, PorAP1.4) or rMenB+OMV NZ is composed of three purified recombinant *Neisseria meningitidis* serogroup B protein antigens, NadA (Neisseria adhesin A) as single protein, NHBA (Neisseria Heparin Binding Antigen) as fusion protein, fHBP (factor H Binding Protein) as fusion protein and PorA P1.4 as the main antigen of Outer Membrane Vesicles (OMV) derived from *Neisseria meningitidis* serogroup B strain NZ 98/254. Antigens are formulated at a dosage of 50 µg for each recombinant protein and 25 µg for the OMV measured as total protein amount, per dose (0.5 mL). This vaccine is a liquid suspension, adjuvanted with aluminium hydroxide and presented as a mono-dose (in a glass syringe) ready for intramuscular injection. The composition of the vaccine is presented in Table 1.

Table 1: Composition of rMenB+OMV NZ vaccine

Active ingredients	Other ingredients
N. meningitidis 961c purified antigen	Aluminium hydroxide
N. meningitidis 936-741 purified antigen	NaCl
N. meningitidis ΔG287-953 purified antigen	Histidine
OMV from *N. meningitidis* strain NZ 98/254	Water for injection

2. Clinical rationale

The development of this Meningococcal group B vaccine is based on two main areas of information relevant to meningococcal disease:

1. The epidemiology of meningococcal disease;
2. The chronology of development of previous meningococcal B vaccines used in response to epidemics in various countries, then developed further with knowledge gained from identification of the genomic structure of the outer membrane proteins of serogroup B.

Invasive meningococcal disease (IMD) occurs worldwide. Incidence varies in different regions of the world. Infants, children, and adolescents are the most vulnerable to developing invasive disease.

Symptoms of the disease occur rapidly and often result in severe outcomes. Despite the availability of medical treatment and effective antibiotics, 8-9% of IMD patients in developed countries die, increasing with age[1], and up to 11-19% of survivors have lifelong sequelae[2]. Each year approximately 1.2 million cases of IMD are recorded worldwide, of which 7,000 occur in Europe[3]. The overall incidence in European countries ranges from approximately one to four cases per 100,000 population[1]. However, during epidemics this may increase to 800 cases or more per 100,000 population.

[1] ECDC surveillance report for 2007 (2010)
[2] Kirsch EA, Barton RP, Kitchen L, and Giroir BP. Phathophysiology, treatment and outcome of meningococcemia: a review and recent experience. *Pediatr Infect Dis J*, 1996; 15:967-79
[3] World Health Organization (WHO), 2001

Over 90% of meningococcal meningitis and septicaemia are caused by five of the 13 meningococcal serogroups, i.e., serogroups A, B, C, W-135 and Y[4]. The introduction of the conjugate serogroup C meningococcal vaccine changed the epidemiology of the disease in developed countries dramatically, leaving serogroup B as the predominant cause of disease. It is thought that the development of vaccines for prevention of serogroup B disease in industrialized nations and serogroup A conjugate vaccines for Africa could lead to global control of meningococcal disease[5].

Serogroup B accounts for a high proportion of meningococcal disease cases in the Americas, Japan and Europe, and Australia (> 80%) and New Zealand (87%)[1]. 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[4]. In Europe, the incidence of disease due to serogroup B is particularly high in Ireland, the United Kingdom, Belgium and Spain. In Europe, the majority of disease occurs in infants under 1 year of age, followed by children through from 1 to 5 years of life. A second peak occurs in adolescents 15 to 19 years of age[1]. The incidence of meningococcal serogroup B disease can increase dramatically during an epidemic. New Zealand experienced an epidemic of group B meningococcal disease with incidence rates of up to 10 times higher than usual, especially affecting the Pacific Islander and Maori populations, where rates increased from 1.6 cases per 100,000 population in 1990 to 17.4 per 100,000 in 2001. Serogroup B epidemics begin slowly but may persist for 10 years or longer, as seen in Cuba, Norway, areas of Chile, and New Zealand[4]. Data from the New Zealand epidemic of meningococcal B disease collected from 1998 to 2003, also showed that the highest rates of disease consistently occurred in those under 5 years of age. In 2003, the rate for children aged less than 1 year was 124.4 per 100,000 population and in children between 1 to 4 years was 59.7 per 100,000 population. In 1999, children under 5 years old represented 56.7% of total cases. Overall, about 80% of disease occurred in those less than 20 years[6]. Within serogroup B strains, most disease is caused by a limited number of groups of genetically related bacteria.

In Australia, invasive meningococcal disease is nationally notifiable. States and territories provide data to the National Notifiable Diseases Surveillance System (NNDSS). NNDSS notifications for meningococcal disease by serogroup for the years 1991-2007 are shown in Figures 1 and 2. Besides NNDSS, reports of meningococcal disease are also collected by the Australian Meningococcal Surveillance Programme (AMSP), which is a national laboratory-based program for the examination of isolates of *Neisseria meningitidis*. AMSP commenced in 1994 through the collaboration of reference laboratories in each jurisdiction and is designed to supplement data from clinical notification schemes. The differences in number of reports between NNDSS and AMSP result from the fact that NNDSS includes probable cases as well as laboratory confirmed cases. Furthermore, not all isolates are sent to AMSP (range 85%-92%[7]).

[4] Girard MP, Preziosi M, Aguado M, and Kieny MP et al. A review of vaccine research and development: Meningococcal disease. *Vaccine*, 2006; 24:4692–4700
[5] Khatami A and Pollard AJ. The epidemiology of meningococcal disease and the impact of vaccines. *Expert Rev. Vaccines*, 2010; 9(3);285–298
[6] Dyet K, Devoy A, McDowell R, Martin D. New Zealand's epidemic of meningococcal disease described using molecular analysis: implications for vaccine delivery. *Vaccine*, 2005; 23:2228–30
[7] NNDSS Annual Report, 2008

Figure 1: NNDSS Notifications for Meningococcal Disease by Serogroup and Year of Diagnosis, Australia, 1991-2007

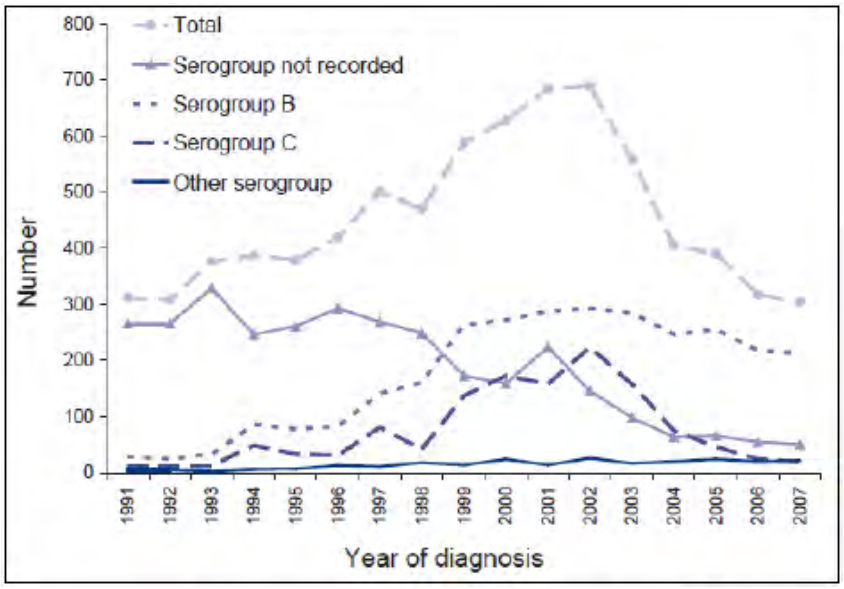
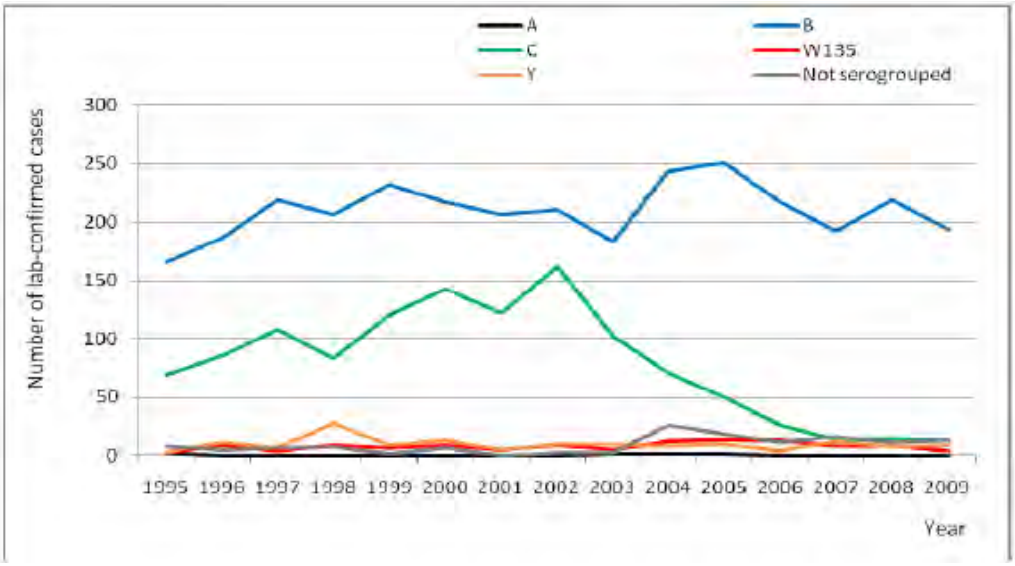


Figure 2 contains data from the AMSP collected over more than a decade in Australian laboratories.

Figure 2. Laboratory-confirmed Cases of IMD by Serogroup, Australia, 1995-2009



Source: AMSP surveillance reports.

These graphs show that the majority of cases of meningococcal disease reported in Australia over the period 1995 to 2009 were due to serogroup B, with the least number of cases due to the serogroups A, W-135 and Y. The data in Figures 3 and 4 also shows the impact that the meningococcal C vaccination program has had on the incidence of disease generally and due to that serogroup: in 2002 41.2% of cases of meningococcal disease were due to serogroup C disease, declining to be only 5.6% in 2009.

Figure 3: Incidence of Laboratory-confirmed Cases of IMD by Serogroup, Australia, 1995-2009

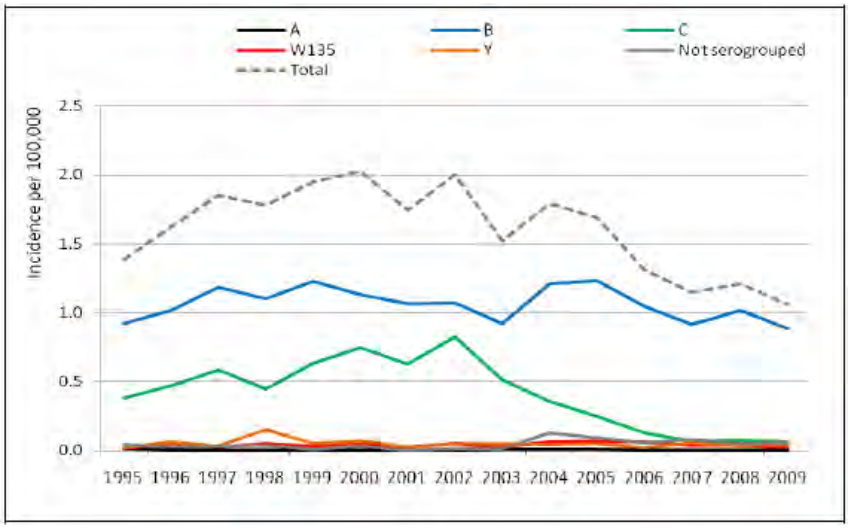
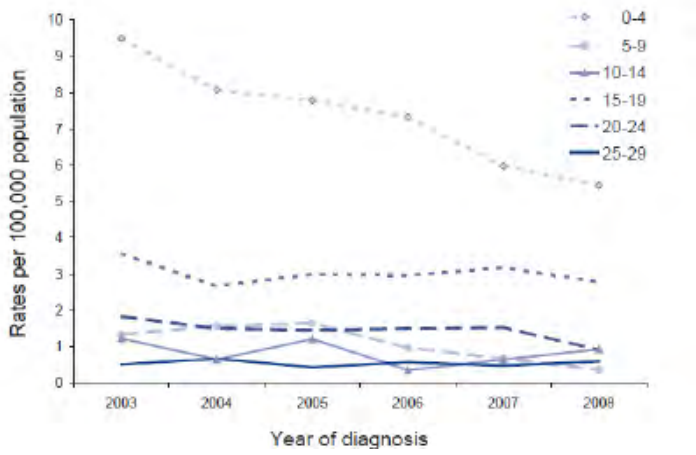


Figure 4: Incidence of IMD serogroup B by age, Australia, 2003-2008



Mortality data from the Australian Bureau of Statistics showed that there were 9 IMD deaths in 2009. Meningococcal disease in Aboriginal and Torres Strait Islander (ATSI) people: across all age groups the incidence of meningococcal disease among the ATSI population was 2.6 times higher among ATSI people compared with non-ATSI people ($p<0.5$) and was highest in 0-4 year olds[8].

The proportion of cases of serogroup B meningococcal disease is 18 percentage points higher among ATSI people compared with non-ATSI ($p=0.001$). Mortality was also higher in this group.

2.1. Meningococcal B subtypes

Data from the Australian Meningococcal Surveillance Program on the phenotypic serotypes of the reported cases of meningococcal B disease for the period 2001 to 2009 are summarized in Table 2 and show that almost half of the cases for which samples were available could not be serotyped. Of the remaining cases, serotype 4 (and/or serotype 4,7) accounted for the majority of cases, with serotype 15, the next most frequent.

[8] Menzies R, Turnour C, Chiu C et al. (2008). "Vaccine preventable diseases and vaccination coverage in Aboriginal and Torres Strait Islander people, Australia 2003 to 2006." *Commun Dis Intell.* 32(Suppl): S2-67.

Table 2: Meningococcal B Serotypes as a Proportion of Cases Available for Serotyping

	2001	2002	2003	2004	2005	2006	2007	2008
Total no. of cases N (%)	N=198	N=202	N=152	N=122	N=144	N=132	N=88	N=103
1	7 (3.5)	13 (6.4)	14 (9.2)	4 (3.3)	10 (6.9)	11 (8.3)	7 (8.0)	10 (9.7)
2	2 (1.0)	0 (0.0)	11 (7.2)	1 (0.8)	0 (0.0)	2 (1.5)	0 (0.0)	0 (0.0)
4	56 (28.3)	58 (28.7)	37 (24.3)	37 (30.3)	24 (16.7)	14 (10.6)	27 (30.7)	15 (14.6)
4,7	0 (0.0)	2 (1.0)	0 (0.0)	0 (0.0)	7 (4.9)	16 (12.1)	0 (0.0)	5 (4.9)
7	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.4)	6 (4.6)	0 (0.0)	7 (6.8)
14	5 (2.5)	5 (2.5)	4 (2.6)	2 (1.6)	6 (4.2)	3 (2.3)	1 (1.1)	6 (5.8)
15	28 (14.1)	35 (17.3)	16 (10.5)	18 (14.8)	27 (18.8)	20 (15.2)	13 (14.8)	18 (17.5)
17,7	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)
19	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (4.2)	3 (2.3)	0 (0.0)	0 (0.0)
19,1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (5.3)	0 (0.0)	4 (3.9)
Not typeable	100 (50.5)	89 (44.1)*	70 (46.1)*	60 (49.2)	58 (40.3)	50 (37.9)	40 (45.5)	38 (36.9)

* Includes six cases in 2002 and five in 2003 for which the type could not be determined.

2.2. Vaccine clinical development program

To date, no broadly effective serogroup B meningococcal vaccines are available. Capsular polysaccharide vaccines have been used for the other meningococcal serogroups but the capsular polysaccharide of meningococcal serogroup B is poorly immunogenic in humans. This prompted research to focus 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. This serogroup B meningococcal vaccine (rMenB+OMV NZ) was developed, based on knowledge gained during vaccine development for the Norwegian (MenBvac) and New Zealand (MeNZB) epidemics, in conjunction with the identification of the *N. meningitidis* serogroup B genome sequence to develop this 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[9].

The first vaccine formulation of the recombinant serogroup B meningococcal vaccine consisted of a single recombinant vaccine antigen, the conserved, recombinant Neisseria Heparin-Binding Antigen (NHBA or 287) formulated with and without OMV derived from *N. meningitidis* Norwegian strain 44/76. This vaccine was safe in clinical studies in healthy adult volunteers; however, to improve immunogenicity and cross-strain protection, the vaccine was redesigned and additional recombinant protein antigens were included in the formulation. To increase the immunogenicity of the antigens, protein-protein fusions of the candidate antigens were generated and vaccines formulated with aluminium hydroxide and with or without OMV derived from either the Norwegian strain 44/76 (OMV NW) or the New Zealand strain NZ98/254 (OMV NZ) were then evaluated in preclinical and clinical studies. The current vaccine formulation (referred to as rMenB+OMV NZ) is based on three proteins: *i)* factor H binding protein (fHBP), *ii)* Neisserial adhesin A (NadA) and *iii)* NHBA or 287.

[9] Pizza M, Scarlato V, Masignani V, Giuliani MM, et al. Identification of vaccine candidates against serogroup B meningococcus by whole-genome sequencing. *Science* 2000; 287:1816–1820.

2.3. Guidance

The process for the selection of the final formulation, dose and timing of vaccinations, conformed to the Committee For Medicinal Products For Human Use Guideline On Clinical Evaluation of New Vaccines (EMEA/CHMP/VWP/164653/2005)[10]. The European Medicines Agency have also sent a list of questions to Novartis regarding the clinical data, to which responses were received [see section 9.3 below for discussion of some of these].

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The clinical studies providing data for this submission are summarised in Table 3.

[10] Accessed on 22/2/12: <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003870.pdf>

Table 3: Overview of Clinical Studies for Australian Application

Study No	Population (Age at Enrollment), Schedule	Type of Study	Country	Vaccine Groups	N enrolled
V72P4	Adults (18-50 y) 0,2,6 months	Phase 2, Multi-Center Open	Italy Germany	**rMenB+OMV NZ** + MenACWY at 6 months	54
V72P5	Adults (18-40 y) 0,1,2 months	Phase 1, Observer blind, Single-center, Randomized	Switzerland	**rMenB+OMV NZ**	28
				rMenB+OMV NW	28
				rMenB	14
V72P6	Infants (2 months) 2,4,6 12, or 12 months	Phase 2, Open label Multicenter Randomized Controlled	UK	rMenB (2,4,6 and 12 months)	48
				rMenB+OMV NZ (2,4,6 and 12 months)	50
				rMenB (12 months only)	25
				rMenB+OMV NZ (12 months only)	24
V72P9	Infants (6-8 months) 0, 2 plus dose at 12 months of age)	Phase 2 Single blind Single center Randomised	UK	rMenB	30
				rMenB+OMV NZ	30
V72P10	Adolescents (11-17 y) 1,2 or 3 doses at 0, 1, 2 months	Phase 2b/3 Observer-blind, Multi-center, Randomized Controlled	Chile	**rMenB+OMV NZ** at month 0, Placebo at month 1 Placebo at month 2	375
				rMenB+OMV NZ at month 0, **rMenB+OMV NZ** at month 1 Placebo at month 2	375
				rMenB+OMV NZ at month 0, Placebo at month 1 **rMenB+OMV NZ** at month 2	380
				rMenB+OMV NZ at month 0, **rMenB+OMV NZ** at month 1 **rMenB+OMV NZ** at month 2	373
				Placebo at month 0, Placebo at month 1 Placebo at month 2	128

Table 3 continued: Overview of Clinical Studies for Australian Application

Study No	Population (Age at Enrollment), Schedule	Type of Study	Country	Vaccine Groups	N enrolled
V72P12	Infants: (2 months) 2,3,4 months, Or 2,4,6 Months.	Phase 2b Open Label, Parallel-group Multi-center Randomized	UK Belgium Germany Czech Rep Italy Spain	**rMenB+OMV NZ** at 2,4,6 months, concomitant routine vaccinations[a]	627
				rMenB+OMV NZ at 2,4,6 months, routine vaccinations at 3,5,7 months	628
				rMenB+OMV NZ at 2,3,4 months, concomitant routine vacinations	318
				Routine vaccinations only at 2,3, 4 months	312
V72P13	Infants (2 months) 2,4,6 months w/6-months f/u	Phase 3 Partially blinded, Multi-Center Randomized Controlled	Italy Germany Austria Czech Rp Finland	**rMenB+OMV NZ** (lot 1) +routine vaccinations	833
				rMenB+OMV NZ (lot2) +routine vaccinations	828
				rMenB+OMV NZ (lot3) +routine vaccinations	820
				Routine vaccinations	659
				MenC+routine vaccinations	490
V72P13 E1	Infants (12 months) Booster (or 2 doses for naive controls)	Phase 3 Open label Multi-Center Extension Study of V72P13	Italy Germany Austria Czech Rp Finland	**rMenB+OMV NZ**+routine (in V72P13 open label subset)/ **rMenB+OMV NZ** and MMRV at 12 months (in V72P13E1)	629
				rMenB+OMV NZ+routine (in V72P13 open label subset)/ **rMenB+OMV NZ** at 12mo, MMRV at 13mo (in V72P13E1)	633
				Routine (in V72P13 open label subset)/MMRV at 12mo, **rMenB+OMV NZ** at 13 and 15 mo (in V72P13E1)	285
				Routine (in V2P13 open label subset)/ **rMenB+OMV NZ** and MMRV at 12mo, **rMenB+OMV NZ** at 14mo (in V72P13E1)	117
				rMenB+OMV NZ + Routine (in V2P13 observer blind subset)/	137

Table 3 continued: Overview of Clinical Studies for Australian Application

Study No	Population (Age at Enrollment), Schedule	Type of Study	Country	Vaccine Groups	N enrolled
				rMenB+OMV NZ and MMRV at 12 months (in V72P13E1)	
				rMenB+OMV NZ + Routine (in V2P13 observer blind subset)/ **rMenB+OMV NZ** at 12mo, MMRV at 13mo (in V72P13E1)	156
				MenC+routine (in V72P13 observer blind subset)/ **rMenB+OMV NZ** and MMRV at 12months (in V72P13E1)	152
				MenC+routine (in V72P13 observer blind subset)/ **rMenB+OMV NZ** at 12mo, MMRV at 13mo (in V72P13E1)	140
V72P13 E2	Infants (24-27 months Persistence after booster, 12 months Persistence after 2 doses and booster dose)	Phase 3 Open label Multi-Center Extension Study of V72P13E1	Czech Rp Finland	**rMenB+OMV NZ**+routine (in V72P13)/ **rMenB+OMV NZ** and MMRV at 12 months (in V72P13E1)	152
				rMenB+OMV NZ+routine (in V72P13)/ **rMenB+OMV NZ** at 12mo, MMRV at 13mo (in V72P13E1)	154
				Routine (in V72P13)/ MMRV at 12mo, **rMenB+OMV NZ** at 13 and 15 mo (in V72P13E1)	67
				Routine (in V2P13 open label subset)/ **rMenB+OMV NZ** and MMRV at 12mo, **rMenB+OMV NZ** at 14mo (in V72P13E1)	19
				New naive subjects, 23-27 months of age, **rMenB+OMV NZ** at 24mo and 26 mo	116

[a] Routine vaccinations: Infanrix Hexa (DTPa-HBV-IPV/Hib) and Prevenar (PCV7)

The submission contained the following clinical information:

- Module 5
  - This contains data from three Phase 1 clinical efficacy studies used in the development of the vaccine, with an earlier formulation and a number of studies using the final vaccine formulation. Using the final formulation, the dossier includes 1 phase 1; 5 phase 2 immunogenicity and safety studies in varying age groups. One Phase 3 immunogenicity and safety study in 11-17 year old population and one Phase 3 immunogenicity, lot consistency and safety study infants with separate report for booster dose after 12 months.

- Module 1
  - Application letter, application form, draft Australian PI and CMI, Australian Labelling and Packaging, Declaration Concerning the Use of Human Embryos or Human Embryonic Stem Cells, Information about the Experts, Good Manufacturing Practice, Overseas Regulatory Status, List of Countries in which a similar application has been submitted, Product Information from CA-NL-NZ-SE-UK-USA, European Summary of Product Characteristics, Risk Management System, Pharmacovigilance System
- Module 2
  - Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.

3.2. Paediatric data

The submission included efficacy (immunogenicity) / safety data in children. Four of the phase 2 studies were in children (from 2 months of age). There were 3 phase 3 studies in children and a phase 2 study in adolescents as well as a phase 2b/3 study in adolescents.

3.3. Good clinical practice

As far as can be verified (and stated explicitly in this submission) all studies complied with good clinical practice. All studies 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.

4. Pharmacokinetics

Pharmacokinetic studies are generally not performed for injectable vaccines, and kinetic properties of vaccines do not provide information useful for establishing adequate dosing recommendations (EMEA/CHMP/VWP/164653/2005)[10].

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

Study V72P5 was the first to evaluate safety and immunogenicity of the final vaccine formulation containing the three recombinant proteins with OMV purified from *N. meningitidis* serogroup B New Zealand strain NZ98/254 (i.e., rMenB+OMV NZ). Healthy adults 18 to 40 years of age received three doses of either rMenB+OMV NZ, rMenB OMV NW or rMenB according to a 0, 1, 2-month schedule. Although all three vaccines were immunogenic with similar safety profiles, the immune response against hypervirulent ST-41/44 complex/lineage III strains was higher in the rMenB+OMV NZ group.

Two Phase 2 studies performed in the UK explored the safety and immunogenicity of rMenB with or without OMV NZ in infants: one (V72P6) when administered to healthy infants at 2, 4 and 6 months of age, followed by a booster at 12 months of age, and one (V72P9) when administered to healthy infants aged 6-8 months at enrolment time, with two doses separated by 2 months, followed by a booster at 12 months of age.

This formulation was selected for further clinical development based on: 1) evidence of enhanced coverage against the hypervirulent ST-41/44 complex/lineage III strains; 2) the

experience in the infant population with Novartis' NZ98/254 OMV-based vaccine, MeNZB, which was shown to be safe and efficacious in the control of the epidemic in New Zealand.

The pivotal Phase 3 study, V72P13 and its extension study V72P13E1, examined the safety and immunogenicity of rMenB+OMV NZ when administered to infants at 2, 4 and 6 months of age with a booster vaccination at 12 months, alongside currently recommended routine vaccinations. This study was conducted in a large population of infants from 5 European countries.

V72P12, a Phase 2b study conducted in infants two months of age on enrolment, was performed in 6 European countries. This study evaluated two differing schedules for rMenB+OMV NZ (a 2, 4, 6- or 2, 3, 4-month schedule) with concomitant or intercalated routine vaccination and showed that antibody responses to rMenB+OMV NZ were similar regardless of the schedule.

V72P10**,** a Phase 2b/3 study of one, two or three rMenB+OMV NZ vaccinations in 11-17-year-old adolescents in Chile, was performed in order to evaluate safety and immunogenicity of the vaccines in adolescents and select the proper vaccination schedule.

The selection of the serum bactericidal assay (SBA) using human complement (h) as the main method for assessing immunogenicity was based on generally accepted scientific method for assessment of human immunity to the meningococcus[11]. 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 vaccine formulation for which approval is sought in this application includes three recombinant protein antigens (fHBP, NadA, and NHBA) and OMV NZ and is referred to throughout this document as rMenB+OMV NZ. The three recombinant vaccine antigens contained in the final selected formulation are:

- 50µg of fHBP, i.e., the recombinant factor H binding protein (derived from MenB strain MC58) fused to accessory protein 936 (derived from MenB strain 2996), or *N. meningitidis* 936-741 purified antigen. The 741 protein (fHBP) binds to factor H, helping the bacterium to evade complement-dependent killing[12].
- 50µg of NadA, i.e., the recombinant Neisseria adhesin A (NadA) (derived from MenB strain 2996), or *N. meningitidis* 961c purified antigen. NadA is involved in adhesion to and penetration into human nasopharyngeal epithelium[13].
- 50µg of NHBA, i.e., the recombinant Neisserial Heparin Binding Antigen (derived from MenB strain NZ98/254) fused to accessory protein 953 (derived from MenB strain 2996), or *N. meningitidis* 287-953 purified antigen. The 287 protein antigen is a target of both meningococcal and human proteases and binds to heparin at an arginine-rich region, suggesting a possible role in serum resistance[14].

The OMV component is:

- 25µg of OMV NZ, i.e., the outer membrane vesicle (OMV) derived from *N. meningitidis*
- serogroup B strain NZ98/254 (New Zealand strain) in which the PorA P1.4 is the immunodominant antigen.

[11] Goldschneider I, Gotschlich EC, Artenstein MS. Human immunity to the meningococcus. I. The role of humoral antibodies. *J. Exp. Med*., 1969; 129(6):1307–26.
[12] Welsh JA, Ram S. Factor H and Neisserial pathogenesis. *Vaccine*, 2008; 26(Suppl 8): I40–I45
[13] Capecchi B, Adu-Bobie J, Di Marcello F, Ciucchi L, et al. Neisseria meningitidis NadA is a new invasin which promotes bacterial adhesion to and penetration into human epithelial cells. *Mol. Microbiol*., 2005; 55(3):687–98
[14] Serruto D, Spadafina T, Ciucchi L, Lewis LA, Ram S, et al. Neisseria meningitides GNA2132, a heparin-binding protein that induces protective immunity in humans. *PNAS*, 2010; 107:3770-75

The vaccine formulation also includes aluminium hydroxide adjuvant (1.5 mg/0.5mL, corresponding to 0.5mg/0.5mL of Al3+).

The EU CHMP had previously agreed to the OMV amount in rMenB+OMV NZ, which is identical in identity and amount to the OMV component present in the MeNZB vaccine and was selected by the Company based on the clinical experience with the New Zealand vaccine. In the same EU Scientific Advice, further justification for the selected amount of recombinant proteins was requested. The recombinant proteins amount (50µg each) was selected based on data from pre-clinical studies in mice together with the experience from other registered vaccines and then confirmed in clinical studies with the rMenB+OMV NZ vaccine.

5.2. Summary of pharmacodynamics

The information in the following summary is derived from immunogenicity and safety studies in humans.

5.2.1. Mechanism of action

The mechanism of action of this vaccine is the induction of protective antibodies. Although the best evidence for its efficacy would be epidemiological data, the standard surrogate marker for the efficacy of vaccines is the induction of specifically related antibodies. So, in terms of measuring immunogenicity, the production of serum bactericidal antibody against the meningococcal B antigens included in this vaccine is used as the correlate of protection.

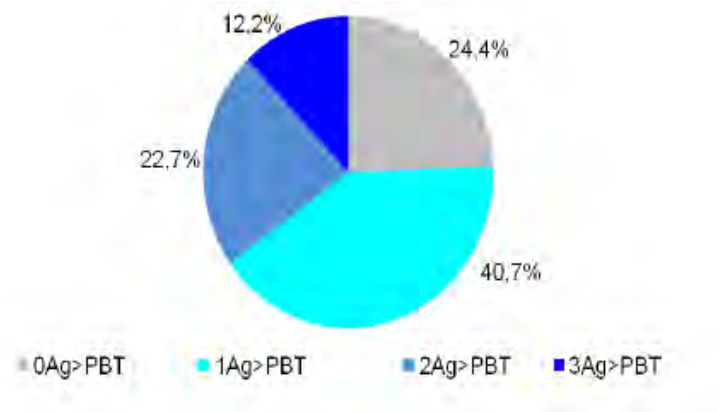
5.2.1.1. Estimation of potential vaccine strain coverage vaccine antigen typing of meningococcal serogroup B strains

To assess the potential breadth of coverage of the MenB vaccine against circulating meningococcal strains within a given population, Novartis first 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. This method is called the "Meningococcal Antigen Typing System" or MATS. Typing of strains for susceptibility to killing by antibodies directed against the vaccine antigens is performed by means of a novel ELISA assay. When the MATS values for each of the 3 recombinant protein antigens (fHBP, NHBA, and NadA) from a collection of invasive isolates are ranked and related to their susceptibility to vaccine-elicited immune sera, a point is observed at which antigen relatedness and/or level of expression is no longer sufficient to support bactericidal killing. Once this threshold (referred to as the "positive bactericidal threshold" or PBT) for a given target age group is identified, vaccine strain coverage estimates can be made on panels of invasive isolates from any given region. Potential strain coverage is therefore defined as the proportion of circulating, endemic strains within a given country or region that score above the PBT for at least one vaccine antigen (fHBP, NadA, NHBA) in MATS analysis or express the PorA P1.4 OMV antigen (evaluated by gene sequencing). These strains would be predicted to be killed by immune sera elicited by the rMenB+OMV NZ vaccine. Based on our MATS analyses of the European strain collections, the overall estimate of strain coverage[3] of all 1052 typeable strains was 78% (95%CI: 64 – 90%). When considering strains predicted to be covered (i.e. those that express levels of any rMenB+OMV NZ antigen above the PBT, 294 strains (27.9%) were covered by a single antigen, while half of the total European collection (529 strains; 50.3%) are predicted to be covered by more than one antigen.

5.2.1.2. Predicted strain coverage in Australia using MATS

The potential of 4CMenB to protect against diverse strains of invasive serogroup B meningococcus isolated in Australia was studied using MATS. A survey of 172 invasive MenB isolates collected during 2009-June 2011 using MATS has been conducted. This analysis revealed that 76% (95% Confidence Interval: 59%-87%) of isolates had an appropriate antigen type to be covered by 4CMenB.

Figure 5: Coverage of Australian 2009-June, 2011 strains by number of 4CMenB vaccine antigens



Of the strains predicted to be covered (n=130), roughly half (60 strains) are covered by more than one antigen. Coverage by more than one antigen provides a measure of redundancy that ensures 4CMenB can still be effective even if one target antigen is mutated or down-regulated.

5.2.2. Pharmacodynamic effects

5.2.2.1. Measurements of immunogenicity

The selection of correlates of protection was based on the US Vaccines and Related Biological Products Advisory Committee (1999)[15] opinion that:

- Immunological correlates can be used to predict efficacy of meningococcal vaccines;
- The presence of bactericidal antibodies can be used as a surrogate marker of protection against meningococcal disease.

Human complement for SBA has been used at a surrogate marker of efficacy in many meningococcal vaccine development programs, such as for the licensing of Menjugate and also the quadrivalent meningococcal conjugate vaccine, Menveo in a number of countries. 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 a response to a request for Scientific Advice, the CHMP agreed that an hSBA ≥1:4 was an appropriate correlate of protection (EMEA/CHMP SA 22 March 07). In later studies, the lower cut-off was changed from 1:4 to 1:5. Using the 1:5 cut-off provided 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 validation of the hSBA assay that has shown that the lower limit of the two-sided 95% confidence interval (CI) for a titer of 1:5 is a titer of 1:4, using linearly interpolated hSBA titres. However hSBAs performed outside the Novartis Marburg laboratory (in this application, study V72P10), the ≥1:4 cut-off was used.

5.2.2.2. Evaluation of bactericidal activity using serogroup B "reference" strains

Novartis has used of a panel of meningococcal serogroup B strains intended to indicate the presence of antigen-specific bactericidal antibody responses (the so-called "reference strains")[16]. The term "reference strain" has also been used in individual clinical study reports and in this document. The strains identified to assess functional immunogenicity induced by the

[15] Accessed at 23/2/12: <http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/bloodvaccinesandotherbiologics/vaccinesandrelatedbiologicalproductsadvisorycommittee/ucm248585.pdf>

[16] Giuliani MM, Biolchi A, Serruto D, Ferlicca F, Vienken K, Oster P, Rappuoli R, Pizza M, Donnelly J, Measuring antigen-specific bactericidal responses to a multicomponent vaccine against serogroup B meningococcus. *Vaccine* 2010; 28:5023-30.

741 (fHBP) antigen (strain 44/76), 961c (NadA) antigen (strain 5/99), and the immunodominant P1.4 PorA component of OMV NZ (strain NZ98/254) are virulent strains of serogroup B meningococci that were isolated from cases of invasive disease. An indicator strain to assess functional immunogenicity against NHBA was identified late in the clinical development program and results are available only for a subset of subjects in Studies V72P12 and V72P13. The use of single strains to assess the functional immunogenicity of each vaccine antigen is considered appropriate by the CHMP[17].

5.2.2.3. Schedule selection

- A 3-dose schedule, administered at least 1 month apart with or without concomitant administration of routine infants vaccines followed by a booster dose in the second year of life is proposed for vaccination of young infants (i.e., age 2 to 5 months) based on data from studies V72P6, V72P12 and V72P13 and its extension V72P13E1.
- A 2-dose schedule administered at least 2-months apart followed by a booster dose in the second year of life (at least 2 months after the last primary vaccination) is proposed for use in unvaccinated older infants between 6 and 11 months of age based on the results of study V72P9.
- A 2-dose schedule administered 2-months apart is recommended for unvaccinated children 12 months to 10 years of age based on data in toddlers from study V72P13E1 as supported by the consistency of the high bactericidal immune response for the younger (toddlers) and older (adolescents) contiguous age groups.
- A 2-dose schedule administered at least 1 month apart is selected for use in adolescents and adults aged 11 years and older based on the results of studies V72P10 in adolescents, and V72P4 and V72P5 in adults.

The studies underpinning these recommendations are briefly discussed in this section, just in terms of the schedule selection, and then in more details in terms of overall efficacy in Section 7.

5.2.2.3.1. Three doses at least 1 month apart in young infants with or without concomitant routine infant vaccines

A 3-dose primary schedule for rMenB+OMV NZ administered with (studies V72P12 and V72P13) and without (study V72P12) concomitant routine vaccinations (Infanrix Hexa and Prevenar) in infants was investigated. The three rMenB+OMV NZ doses were administered at 2,4,6, months of age (2,4,6 schedule) or at 2,3,4 months of age (2,3,4 schedule) to offer more flexibility in the indication and in the vaccine utilization. Immune responses to three doses of rMenB+OMV NZ administered at 2, 4, 6 months with or without concomitant routine vaccinations (in the latter group routine vaccinations were given non concomitantly at 3,5,7 months) as measured at one month after the third rMenB+OMV NZ vaccination are presented in Table 4 (Study V72P12). The response at one month after the 3rd rMenB+OMV NZ dose as assessed by hSBA GMTs and percentage of subjects achieving a hSBA ≥1:5 was remarkably similar across studies for subjects receiving a 2,4,6 schedule regardless of concomitant routine vaccinations (Table 4, first three columns). Subjects with hSBA ≥1:5 were 100% for strain 44/76, ranged from 99% to 100% for strain 5/99, and from 79% to 87% for strain NZ98/254. Antibody titres to the NHBA vaccine antigen were also high as measured by ELISA GMCs in both infant studies. Consistent with this, 84% of the subjects from study V72P13 tested by hSBA against the newly identified reference strain (M10713) for the NHBA vaccine antigen showed a titer ≥1:5 (Table 5). Overall the immune responses at one month after the third vaccination as measured by hSBA in terms of percentages of subjects with a titer ≥1:5 and of GMTs for the three reference strains 44/76, 5/99, NZ98/254 and by ELISA GMCs for the rMenB+OMV NZ NHBA vaccine antigen were very similar between subjects who received the 2, 3, 4 schedule

[17] EMEA/CHMP SA, 22 March 2007; EMEA/CHMP Follow-Up SA, 18 December 2008

with concomitant routine vaccines and the subjects who received a 2, 4, 6 schedule (Table 4). In particular, as required by the protocol pre-specified primary immunogenicity objectives of studies V72P12 andV72P13, the lower limit of the 2-sided 95% CI for the percentages of subjects with an hSBA ≥1:5 was ≥70% for each of the 3 reference strains.

Table 4: Responses to rMenB+OMV NZ After a 3-dose Primary Schedule in Infants from 2 Months of Age With and Without Concomitant Routine Infant Vaccines – (PP population)

		V72P13	V72P12		
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 (non concomitant)	2,3,4 with concomitant routine vaccinations
44/76	% 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
	hSBA GMT (95%CI)	91 (87-95) N=1149	86 (80-92) N=525	113 (105-121) N=534	82 (75-91) N=273
	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
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
	hSBA GMT (95%CI)	635 (606-665) N=1152	537 (494-584) N=527	699 (643-759) N=529	325 (292-362) N=275
	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
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
	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
	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
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
	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

Table 5: Immune Responses to the Newly Identified Reference Strain for NHBA Vaccine Protein in Infants and Toddlers – (MITT Population)

Reference Strain		V72P13 2,4,6 with concomitant routine vaccinations N=100[a]	V72P13E1 Booster (12B12M (1a) and 12B13M (1b))[b] N=100[a]
M10713	% hSBA≥1:5 (95% CI)	84 (84%) (75-91)	98 (98%) (93-100)
	hSBA GMT (95%CI)	16[c] (13-21)	42[d] (36-50)
	hSBA GMR (95% CI)	5.22[e] (3.78-7.22)	-

5.2.2.3.2. Unvaccinated infants 6 to 11 months of age

The recommended schedule for previously unvaccinated infants of 6 to 8 months of age is 2 vaccinations with rMenB+OMV NZ with an interval of at least 2 months between doses. A booster dose is recommended in the second year of life at least 2 months after the second primary dose. This recommendation is based on data from study V72P9. In this study, 27 healthy infants aged 6 to 8 months received 2 vaccinations with rMenB+OMV NZ at months 0, 2 of the study with an additional dose at 12 months of age. One month after the second

vaccination, hSBA ≥ 1:4 were achieved by 100% of subjects against strains 44/76 and 5/99, and 95% against NZ98/254. These percentages were almost unchanged one month after the third vaccination (100%, 100% and 96%), suggesting that two vaccinations with the selected formulation were sufficient to produce the required response against the reference strains in this age group. There were marked increases in hSBA GMTs at one month after the second vaccination against all three strains, with further increases for strains 5/99 and NZ98/254 (but not 44/76) after a booster dose at 12 months of age. It was concluded that a third vaccination is not warranted for the primary series, but may be considered as a booster dose in the second year of life as the GMTs are further enhanced with a subsequent dose.

5.2.2.3.3. Booster dose

Study V72P13E1 investigated the safety and immunogenicity of a 12-month booster administered with or without concomitant MMRV vaccination, in infants who had previously received three doses of rMenB+OMV NZ at 2, 4 and 6 months of age in parent study V72P13. Persistence of bactericidal antibodies at 12 months of age prior to the booster was also evaluated V72P13E1. Responses to the booster dose were robust for all strains, with 100% of the subjects achieving hSBA ≥1:5 against strains 44/76 and 5/99, and 94%-97% of subjects against strain NZ98/254 (Table 6).

Table 6: Number (%) of Subjects with hSBA ≥ 1:5 at 1 Month After Booster Vaccination With or Without MMRV- PP Population, V72P13E1

Strain	44/76		5/99		NZ98/254	
Group	12B12M[a]	12B13M[b]	12B12M[a]	12B13M[b]	12B12M[a]	12B13M[b]
	N=211	N=215	N=210	N=213	N=211	N=215
Baseline	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 immune response to the booster dose of rMenB+OMV NZ was also assessed by evaluating hSBA GMTs at one month after the booster. Persistence of responses at 12 months after the booster vaccination was demonstrated in the extension study V72P13E2, as measured by both the percentage of subjects with hSBA ≥1:5 and hSBA GMTs (Table 7). These analyses were performed on the MITT population, and included hSBA data for the fourth reference strain M10713: see Table 7.

Table 7: Evaluation of One Year Antibody Persistence Post Booster Dose as Measured by Percentage of Subjects with hSBA ≥ 1:5, and hSBA GMTs, in 24-Month-Old Toddlers previously Vaccinated at 2, 4, 6 and 12 Months of Age - MITT Population, V72P13E2

	44/76		5/99		NZ98/254		M10713	
	1a B246_12M12	1b B246_12M13	1a B246_12M12	1b B246_12M13	1a B246_12M12	1b B246_12M13	1a B246_12M12	1b B246_12M13
	N=147	N=152	N=147	N=151	N=147	N=153	N=143	N=148
hSBA ≥ 1:5								
1 Month after Booster	148 (100%) (98-100) N=148	152 (100%) (98-100) N=152	148 (100%) (98-100) N=148	152 (100%) (98-100) N=152	142 (96%) (91-98) N=148	142 (93%) (88-96) N=153	28 (97%) (82-100) N=29	35 (97%) (85-100) N=36
12 Months after Booster	88 (60%) (51-68)	97 (64%) (56-71)	141 (96%) (91-98)	149 (99%) (95-100)	26 (18%) (12-25)	26 (17%) (11-24)	57 (40%) (32-48)	48 (32%) (25-41)
GMTs								
1 Month after Booster	148 (121-180)	125 (101-153)	1377 (1139-1665)	1336 (1097-1628)	37 (28-50)	29 (22-38)	40 26-63 N=29	33 21-53 N=36
12 Months after Booster	7.38 (5.55-9.83) N=147	8.3 (6.17-11)	68 (52-91) N=147	90 (67-121) N=151	1.57 (1.24-1.99) N=147	1.79 (1.4-2.29)	4.34 (3.21-5.87)	3.61 (2.63-4.94)

5.2.2.3.4. Unvaccinated children in the second year of life

The vaccination schedule consists of two doses with an interval of at least 2 months between doses. The need for a booster dose after this vaccination schedule has not been established. This recommendation is based on date from study V72P13E1 which evaluated the immunogenicity of a two-dose schedule of rMenB+OMV NZ given at 13 and 15 months or 12 and 14 months to naïve toddlers. Immmunogenicity was measured by percentage of subjects with hSBA ≥ 1:5 one month after the second dose (Table 8). One month after both the two-dose schedules, percentages of subjects with hSBA ≥1:5 were 100% and 100% for strain 44/76; 100% and 100% for strain 5/99; 100% and 96% for strain NZ98/254 in the respective two-dose schedules. It can be concluded that a 2- dose schedule administered at either 12 and 14 months or 13 and 15 months of age produces an adequate immune response in naive subjects.

Table 8: % of subjects with hSBA ≥ 1:5 one month after a 2 dose (given at 13 and 15 months or 12 and 14 months) schedule of rMenB+OMV NZ in unprimed toddlers - PP Population

	44/76		5/99		NZ98/254		M10713	
	1a B246_12M12	1b B246_12M13	1a B246_12M12	1b B246_12M13	1a B246_12M12	1b B246_12M13	1a B246_12M12	1b B246_12M13
	N=147	N=152	N=147	N=151	N=147	N=153	N=143	N=148
	hSBA ≥ 1:5							
1 Month after Booster	148 (100%) (98-100) N=148	152 (100%) (98-100) N=152	148 (100%) (98-100) N=148	152 (100%) (98-100) N=152	142 (96%) (91-98) N=148	142 (93%) (88-96) N=153	28 (97%) (82-100) N=29	35 (97%) (85-100) N=36
12 Months after Booster	88 (60%) (51-68)	97 (64%) (56-71)	141 (96%) (91-98)	149 (99%) (95-100)	26 (18%) (12-25)	26 (17%) (11-24)	57 (40%) (32-48)	48 (32%) (25-41)
	GMTs							
1 Month after Booster	148 (121-180)	125 (101-153)	1377 (1139-1665)	1336 (1097-1628)	37 (28-50)	29 (22-38)	40 26-63 N=29	33 21-53 N=36
12 Months after Booster	7.38 (5.55-9.83) N=147	8.3 (6.17-11)	68 (52-91) N=147	90 (67-121) N=151	1.57 (1.24-1.99) N=147	1.79 (1.4-2.29)	4.34 (3.21-5.87)	3.61 (2.63-4.94)

Immmunogenicity was also measured using hSBA GMTs. One month after the two-dose schedules, hSBA titres increased significantly. Naive toddlers at 12 months of age very rarely had bactericidal antibodies and the increase in hSBA titres for the three reference strains was similar for both the 13 and 15 months or 12 and 14 months dose schedules (GMTs 271 and 248 for strain 44/76; 599 and 627 for strain 5/99; 43 and 32 for strain NZ98/254 in the respective two-dose schedules). Persistence of responses at 12 months after this two-dose schedule of vaccination was demonstrated in the extension study V72P13E2, as measured by both the percentages of subjects with hSBA ≥1:5 and hSBA GMTs (Table 9). These analyses were performed on the MITT population, and included hSBA data for the fourth reference strain M10713.

Table 9: Evaluation of One Year Antibody Persistence Measured by % of Subjects with hSBA ≥ 1:5, and hSBA GMTs, in 2-Dose Catch-up Primed Toddlers - MITT Population, V72P13E2

	44/76		5/99		NZ98/254		M10713	
	2a B13_15_27	2b B12_14_26	2a B13_15_27	2b B12_14_26	2a B13_15_27	2b B12_14_26	2a B13_15_27	2b B12_14_26
	N=68	N=18	N=68	N=18	N=68	N=18	N=65	N=18
	hSBA ≥ 1:5							
1 Month after 2nd Vaccination	66 (100%) (95-100) N=66	18 (100%) (81-100)	66 (100%) (95-100) N=66	18 (100%) (81-100)	66 (100%) (95-100) N=66	17 (94%) (73-100)	10 (71%) (42-92) N=14	5 (71%) (29-96) N=7
12 Months after 2nd Vaccination	50 (74%) (61-83)	10 (56%) (31-78)	66 (97%) (90-100)	17 (94%) 73%-100%	12 (18%) 9%-29%	1 (6%) 0%-27%	25 (38%) 27%-51%	5 (28%) (10-53)
	GMTs							
1 Month after 2nd Vaccination	339 (237-484) N=66	241 (142-409)	726 (496-1064) N=66	647 (367-1144)	47 (33-68) N=66	33 (19-56)	15 (4.17-54) N=14	16 (5.66-48) N=7
12 Months after 2nd Vaccination	14 (8.63-22)	7.97 (3.95-16)	70 (42-116)	68 (31-146)	1.67 (1.11-2.52)	1.2 (0.65-2.24)	3.7 (2.15-6.35)	3.25 (1.43-7.36)

5.2.2.3.5. Subjects 11 years of age and over

The recommended dosage schedule for individuals 11 years of age and over and for adults is 2 vaccinations with rMenB+OMV NZ, separated by at least one month. This is based on the following studies:

In adolescents (11-17 years of age), multiple vaccination schedules for the rMenB+OMV NZ vaccine were assessed in study V72P10. Results up to 4 months after the first injection, compared one dose at month 0 (group rMenB0, N=336) to 2 doses at months 0 and 1 (group rMenB01, N=344) or months 0 and 2 (group rMenB02, N=342) to 3 doses at months 0, 1 and 2 (group rMenB012, N=335). Results up to 12 months[18] after the first assessed 2 doses at months 0 and 6 (group rMenB06, N=128). The vaccination schedules of two doses administered with an interval of one or two months (rMenB01 and rMenB02) showed a similarly high immune response: as can be seen in Table 10, 99% to 100% of subjects achieved hSBA ≥1:4 against the 44/76, 5/99 and NZ98/254 reference strains after both of these two-dose schedules. In the combined group that received one dose of the vaccine (group Dose 0, N=1357), although most of the subjects showed hSBA ≥1:4, the response was relatively lower (92% to 97% across the strains) compared to the two-dose schedules. The three dose vaccine schedule provided no added immune response in terms of percentages of subjects with hSBA >1:4.

[18] Sponsor clarification: only safety data are available at 12 months

Table 10: Percentages (95% CI) of Subjects Aged 11 to 17 Years With hSBA ≥ 1:4 After Each Vaccination By Strain – PP Population, V72P10

		rMenB0	rMenB01	rMenB02	rMenB012	Placebo	Dose 0[a]	Dose 01[b]
Strain 44/76-SL		N=336	N=344	N=342	N=335	N=116	N=1357	N=679
	Month 0	46% (40-51)	39% (34-44)	44% (38-49)	46% (41-52)	46% (36-55)	44% (41-46)	43% (39-46)
	Month 1	**92%** (89-95)	93% (90-96)	92% (88-94)	95% (92-97) N=334	43% (34-53) N=115	93% (92-94) N=1356	94% (92-96) N=678
	Month 2	91% (87-94) N=322	**100%** (99-100) N=330	89% (85-92) N=324	100% (98-100) N=308	50% (40-59) N=109	NA	100% (99-100) N=638
	Month 3	86% (82-90) N=316	99% (98-100) N=320	**100%** (99-100) N=319	**100%** (98-100) N=304	48% (38-58) N=108	NA	NA
Strain 5/99		N=336	N=344	N=342	N=335	N=116	N=1357	N=679
	Month 0	37% (32-43)	30% (25-35)	35% (30-40)	36% (30-41)	29% (21-38)	34% (32-37)	33% (29-37)
	Month 1	**97%** (94-98) N=335	97% (94-98)	96% (94-98)	97% (94-98) N=334	35% (26-44) N=115	97% (96-98) N=1355	97% (95-98) N=678
	Month 2	94% (91-97) N=322	**100%** (99-100) N=330	93% (90-96) N=324	100% (98-100) N=309	31% (23-41) N=109	NA	100% (99-100) N=639
	Month 3	90% (86-93) N=317	100% (98-100) N=320	**99%** (98-100) N=320	**100%** (99-100) N=304	32% (24-42) N=108	NA	NA
Strain NZ98/254		N=336	N=344	N=342	N=334	N=116	N=1356	N=678
	Month 0	37% (32-42)	34% (29-39)	36% (31-41)	33% (28-38)	38% (29-47)	35% (32-38)	33% (30-37)
	Month 1	**93%** (89-95) N=335	94% (91-96)	92% (88-94)	95% (92-97)	38% (29-48) N=115	93% (92-94) N=1355	94% (92-96)
	Month 2	83% (78-87) N=321	**100%** (98-100) N=330	83% (78-87) N=323	100% (98-100) N=309	39% (29-48) N=109	NA	100% (99-100) N=639
	Month 3	78% (73-82) N=316	97% (95-99) N=320	**100%** (99-100) N=319	**99%** (97-100) N=303	43% (33-52) N=108	NA	NA

High GMTs were generated after both two-dose schedules. Compared to the single dose rMenB0 group, GMTs were significantly higher for the groups receiving two and there was no increase in GMTs following a third dose. A third dose in the primary series is therefore not warranted in this age group. The response to 2 doses of rMenB+OMV NZ given 6 months apart was investigated in group rMenB06 (Table 11). This vaccination schedule showed a similarly high immune response to that of two doses administered with an interval of one or two months.

Table 11: Percentages (95% CI) of Subjects 11 to 17 Years With hSBA≥ 1:4, Vaccinations at 0 and 6 Months (Group rMenB06), by Strain – PP Population, V72P10

	44/76	5/99	NZ98/254
Month 0	42% (33-52) N=112	29% (20-38) N=112	32% (24-42) N=112
Month 1	**92%** **(85-96)** **N=112**	**97%** **(92-99)** **N=111**	**90%** **(83-95)** **N=111**
Month 2	88% (80-93) N=108	95% (90-98) N=108	81% (73-88) N=107
Month 3	84% (76-90) N=107	92% (85-96) N=107	80% (72-87) N=107
Month 6	76% (66-84) N=100	79% (70-87) N=100	81% (72-88) N=99
Month 7	**100%** **(96-100)** **N=86**	**99%** **(94-100)** **N=86**	**100%** **(96-100)** **N=86**

In adults, the rMenB+OMV NZ formulation has been tested in the smaller study V72P5: 28 healthy subjects aged 18 to 40 years were enrolled to receive 3 vaccinations with rMenB+OMV NZ at months 0, 1 and 2. Blood was taken for immunogenicity measurements at baseline, and at one month after the second and third vaccinations. One month after the second vaccination, hSBA ≥ 1:4 were assessed against a panel of 15 *N meningitidis* serogroup B strains, including the reference strains. All subjects (100%) had hSBA ≥ 1:4 against strains 44/76 and 5/99, and 96% had hSBA ≥ 1:4 against strain NZ98/254. There was no improvement in percentages of subjects with hSBA ≥ 1:4 after a third vaccination, suggesting that two vaccinations were sufficient to produce the required response against the reference strains in this age group.

5.2.2.3.6. Subjects 2 to 10 years of age

This application does not contain immunogenicity data from subjects aged 2 to 10 years, Novartis recommend that a similar two-dose vaccination schedule is supported by the currently available data. Based on the burden of disease and other epidemiologic factors (e.g., carriage rates in adolescents), the initially targeted age groups for study were infants and toddlers below 2 years of age and adolescents 11 years of age and above and adults. An additional study in 2 to 10 year old children is planned (V72_28) and data would be available post-licensure. Results from studies in older infants (V72P9), toddlers (V72P13E1), adolescents (V72P10) and adults (V72P5) offer a very clear and consistent outcome: as measured by subjects with hSBA ≥ 1:5, response rates are similarly very high after a two dose vaccination schedule beginning from as young as 6 months of age as when the two dose series is administered to adolescents and adults. Importantly, the hSBA GMTs after the 2nd dose in these age groups are also very high and comparable across the age group spectrum (Table 12).

Table 12: hSBA GMTs (95% CI) Across Studies in Naive Subjects 6 months to 17 years of age - One Month after a Two dose Schedule of rMenB+OMV NZ - PP Populations

Age		6 to 8 months	12 to 15 months		11-17 years
Strain		V72P9	V72P13E1		V72P10
		rMenB+OMV NZ at 6-8 and 8-10 months of age	rMenB+OMV NZ at 13 and 15 months of age	rMenB+OMV NZ at 12 and 14 months of age	All subjects receiving 2 vaccinations 1 month apart
44/76	Baseline	1.70 (1.29-2.24) N=24	1.24 (1.15-1.35) N=161	1.22 (1.07-1.38) N=67	3.89 (3.45-4.4) N=679
	1 month after 2nd Vaccination	250 (173-361) N=23	271 (237-310) N=163	248 (201-306) N=67	210(193-229) N=638
5/99	Baseline	1.05 (0.98-1.12) N=24	1.06 (1-1.13) N=160	1.03 (0.94-1.13) N=67	2.64 (2.38-2.92) N=679
	1 month after 2nd Vaccination	534 (395-721) N=23	599 (520-690) N=164	627 (502-783) N=67	490 (455-528) N=639
NZ98/254	Baseline	1.00 (1.00-1.00) N=24	1.03 (0.98-1.07) N=162	1.03 (0.97-1.1) N=67	3 (2.66-3.39) N=678
	1 month after 2nd Vaccination	27 (21-36) N=22	43 (38-49) N=164	31 (25-38) N=67	92 (84-102) N=639

5.3. Evaluator's overall conclusions on pharmacodynamics

The selection of antigens, dose and vaccine composition is based on both clinical experience and data collected prior to the studies included in this application. The studies discussed briefly above are discussed more fully in Section 7 (efficacy). In this section, they are discussed in relation to the choice of vaccination schedules. As well as showing efficacy in all studies, the studies in infants under 6 months, had best results after 3 vaccinations, but it did not affect efficacy, whether the schedule was 2, 3, 4 months or 2, 4, 6 months and also, whether they were given separately or concomitantly with other childhood vaccines. This data is very helpful in that it provides flexibility in terms of recommendations. The easiest way to administer this vaccine will probably be concomitantly with other vaccines. The responses waned over 6 months, and then greatly benefited from a booster at 12 months. The studies in the infants/toddlers over 6 months show that a two-dose regimen (2 months apart) is sufficient, with little benefit from a third primary dose, although there was benefit from a booster in the second year of life. In the older groups (11 years and on), two doses (2 months apart) were sufficient (and better than one dose) and there was no added benefit from a third dose. In adolescents, it didn't matter whether these two vaccinations were given 1 month apart, 2 months apart or 6 months apart. It is important to note that there is no data in children 2-10 years (but a clinical study in this age group is planned).

6. Dosage selection for the pivotal studies

The formulation selection is discussed above in Section 5.1. Both the pivotal and other efficacy studies were involved in determining the optimal schedule selection for marketing application. The studies used in the development program leading up to the selection of schedules for the pivotal studies are briefly described here.

6.1. Clinical study V72P4

This was a Phase 2, open-label, multi-centre study in healthy at-risk adults (18 to 50 years of age) routinely exposed to *N meningitidis*, designed to explore the immunogenicity and safety of three doses of rMenB+OMV NZ given at 0, 2 and 6 months (and to explore the immunogenicity of a single dose of Novartis MenACWY conjugate vaccine given at 6 months concomitantly with the third rMenB+OMV NZ vaccination). rMenB+OMV NZ formulation effectively induced bactericidal antibodies in adults following two doses at 0 and 2 months as measured by hSBA against the three reference strains 44/76, 5/99 and NZ98/254. A third dose at 6 months did not produce any further benefit.

6.2. Clinical study V72P5

This phase 1 study was designed to obtain preliminary data in healthy adults (18 to 40 years of age, N=70) on the similarity of the safety profiles and the similarity of the humoral immune responses, as measured by hSBA and ELISA, of the addition of the Norwegian or the New Zealand OMVs to the Novartis Meningococcal B Recombinant Vaccine. In the rMenB+OMV NZ group and the rMenB+OMV NW group, the proportion of subjects with hSBA ≥ 1:4 increased from baseline to 1 month after the third vaccination for 14 of the 15 tested *N meningitidis* serogroup B strains; in the rMenB group, this was the case for 13 of the strains. Against strains 44/76, and 5/99 all (100%) subjects in all vaccine groups had achieved hSBA ≥ 1:4 at 1 month after the second vaccination. Against strain NZ98/254, 96% of the subjects in the rMenB+OMV NZ group achieved hSBA ≥1:4 against at 1 month after the second dose while this percentage was lower in the rMenB+OMV NW group (74%) and in the MenB group (69%). These results encouraged the further development of the rMenB+OMV NZ strain.

6.3. Clinical study V72P6

This was a phase 2, open label, multi-centre, controlled, randomized study, the first to be conducted in healthy infants aged 2 months at time of enrolment. Subjects received rMenB or rMenB+OMV NZ vaccinations intramuscularly either according to a 2, 4, 6 and 12 months of age immunization schedule, or as a single dose at 12 months of age. The immunogenicity results demonstrated that rMenB+OMV NZ could effectively induce bactericidal antibodies in infants following three doses at 2, 4 and 6 months of age, as measured by hSBA against the three MenB strains 44/76, 5/99 and NZ98/254. Bactericidal antibody was also found to persist against the three vaccine antigens at 12 months of age, 6 months after the primary series, but the percentages of subjects with hSBA ≥1:4 had fallen from 87% at 1 month after the third vaccination to 68% at 12 months of age for strain 44/76, from 95% to 88% for strain 5/99, and from85% to 36% for strain NZ98/254, demonstrating the need for a booster dose. The responses could be further boosted with a 4th dose of rMenB+OMV NZ at 12 months of age, demonstrating that the infants had been primed with the three doses and immunological memory had been generated. The control subjects in this study who received a single dose of rMenB+OMV NZ vaccine at 12 months of age served as comparators for the 12-month booster response in the subjects receiving the vaccine at 2, 4 and 6 months. The proportion of subjects achieving hSBA ≥1:4 against the three reference strains was consistently lower for the control subjects receiving a single dose at 12 months of age as compared to the fourth dose response in the rMenB+OMV NZ subjects group at the same age (73% versus 100% for strain 44/76, 73% versus 97% for strain 5/99, and 18% versus 94% for strain NZ98/254). This study suggested that a 3 dose primary course was required in 2-month-old infants, a booster dose was required after the primary course, and that one vaccination was insufficient in naive infants of 12 months of age and above. The study provided sufficient evidence to warrant the further development and evaluation of the rMenB+OMV NZ vaccine in phase 3.

7. Clinical efficacy

- **Studies providing efficacy data**

There are nine studies included in this application to support the immunogenicity of the vaccine: 3 studies (V72P10, V72P4, and V72P5) in subjects 11 years of age and older (adolescents 11 to 17 years of age and adults 18 to 50 years of age) and 6 studies (V72P13, V72P13E1, V72P13E2, V72P12, V72P9, and V72P6) in the infant and toddler populations. Data are available for 1622 exposed (from 1631 enrolled) adolescent subjects 11 to 17 years of age, 81 adult subjects 18 to 50 years of age, and 4843 infant subjects 2 to 23 months of age exposed to at least one dose of the rMenB+OMV NZ vaccine.

- **Studies in adolescents and adults:**
  - V72P10 was a pivotal phase 2b/3 study in this age group assessing various vaccination schedules conducted in Chile in 1631 adolescents 11 to 17 years of age.
  - V72P4 was a phase 2, open-label study conducted in Italy and Germany on 54 [53 vaccinated] laboratory workers aged 18 to 50 years who were routinely exposed to *N. meningitidis*
  - V72P5 was a phase 1 study conducted in Switzerland in 70 adults 18 to 40 years of age.
- **Studies in infants:**
  - V72P13 was a pivotal, phase 3, lot comparison and non-interference study conducted in Italy, Germany, Austria, Finland and the Czech Republic in 3630 infants aged 2 months at entry.
  - V72P13E1 was the extension study to the above, investigating booster response and non-interference with routine MMRV vaccination in 2249 toddlers in their second year of life
  - V72P13E2 was an extension study of V72P13E1 and enrolled 508 subjects, comprising 392 subjects who had participated in the open-label, immunogenicity subset conducted in Finland and the Czech Republic. The study investigated antibody persistence one year after the booster dose given in V72P13E1, and booster response in toddlers one year after a 2-dose schedule administered in the second year of life. An additional group of 116 naïve subjects (defined as subjects who had never previously received any meningococcal B vaccine) approximately 24 months of age were recruited at the same study sites.
  - V72P12 was a phase 2b study comparing different vaccination schedules and non-interference with routine vaccinations, conducted in the UK, Spain, Italy, Belgium, Germany and Czech Republic, in 1885 infants aged 2 months at entry.
  - V72P9 was a phase 2 study conducted in the UK in 60 infants aged 6-8 months at entry.
  - V72P6 was a phase 2 study conducted in the UK in 147 infants aged 2 months at entry.

In all studies, responses in vaccine recipients were measured by a serum bactericidal assay using human complement (hSBA) as a correlate of clinical efficacy against serogroup B meningococcus. Serum was collected just before vaccination (study day 1), and at 30 days after the last vaccination in all studies. Serum was also collected 30 days after the second vaccination in studies V72P5, V72P6 and V72P9, and 30 days after every vaccination in studies V72P4 and V72P10. In study V72P13E1, serum was also collected and analysed six months after the third vaccination in parent study V72P13 to assess antibody persistence after the primary infant vaccination course.

· **Correlates of protection**

As described in Section 4, the licensure of meningococcal vaccines has been based on a serological surrogate marker for protection, human bactericidal antibody (hSBA). The primary endpoint of studies contained within this application is the proportion of subjects with hSBA titres equal to or above the threshold of 1:4 against each of the three reference meningococcal serogroup B strains (Table 13). The use of this threshold is based on the work by Goldschneider[11] 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 titres ≥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[19]. It was then modified to ≥ 5 to provide a more conservative measure. The standards used in this application are those deemed acceptable to the EU CHMP (EMEA/H/SA/834/1/2006/III). The use of single strains to assess the functional immunogenicity of each vaccine antigen was considered appropriate by the EU CHMP (EMEA/H/SA/834/1/2006/III, follow-up EMEA//H/SA/834/1/FU/1/2007/III, and follow-up EMEA/H/SA/384/1/FU/3/2008/III).

Table 13: Immunogenicity Endpoints – rMenB-OMV NZ hSBA

Endpoint	Endpoint definitions
≥1:4 or ≥1:5	Percentage of subjects achieving this hSBA cut-off
≥1:8	Percentage of subjects achieving this hSBA cut-off
≥Fourfold increase	Percentage of subjects with at least fourfold increase from baseline in hSBA titer: Titers below the limit of detection were set to half the limit of detection for the purpose of analysis
GMT	Geometric mean hSBA titer
GMR	Geometric mean ratio
ELISA for 287-953 antigen	Geometric mean ELISA titer

The immunogenicity endpoints used to assess the impact of this vaccine on vaccination with other routine childhood vaccinations are summarised in Table 14. For the three pertussis antigens, GMCs and 4-fold increases from baseline were also evaluated as endpoints.

[19] Holst J, Feiring B, Fuglesand J. E, Hoiby E.A, Nokleby H, Aaberge I.S, Rosenqvist E. Serum bactericidal correlates with the vaccine efficacy of outer membrane vesicle vaccines against Neisseria meningitidis serogroup B disease. *Vaccine* (2003) 21:734-737.

Table 14: Immunogenicity Endpoints - Routine Infant Vaccinations

Vaccine	Test	Antigens	Cut-off level
InfanrixHexa	ELISA	Diphtheria (D)	≥0.1 IU/mL and ≥1.0 IU/mL
	ELISA	Tetanus (T)	≥ 0.1 IU/mL and ≥ 1.0 IU/mL
	ELISA	Pertussis toxin (PT) FHA Pertactin	Seroconversion defined as either 1) a ≥4-fold increase for each pertussis antigen in those subjects seronegative at baseline or 2) in those initially seropositive, persistence of the pre-vaccination antibody concentration at least at the same antibody concentration as before vaccination, taking into account the decay of maternal antibodies.
	Viral Neutralizing Test (NT)	Poliovirus type 1 Poliovirus type 2 Poliovirus type 3	≥ 1:8
	ELISA	Hep B (HBV)	≥ 10 mIU/mL
	ELISA	PRP-Hib	≥ 0.15 µg/mL and ≥ 1.0 µg/mL
Prevenar	ELISA	PnC 4 PnC 6B PnC 9V PnC 14 PnC 18C PnC 19F PnC 23F	≥ 0.35 µg/mL
Priorix-Tetra	ELISA	Measles Mumps Rubella Varicella	≥ 255 mIU/mL ≥ 10 ELISA Ab units/mL ≥ 10 IU/mL ≥ 1.25 gpELISA units/mL (seroconversion) ≥ 5 gpELISA units/mL (seroprotection)

7.1. BEXSERO (rMenB+OMV NZ) for active immunization against invasive disease caused by *N. meningitidis* of individuals from 2 months of age and older.

7.1.1. Pivotal efficacy studies

The pivotal study in adolescents was V72P10 and in infants/toddlers it was V72P13.

7.1.1.1. V72P13

7.1.1.1.1. Study design, objectives, locations and dates

V72P13 was a Phase 3, partially blinded, multi-centre, controlled, randomized study conducted in Italy, Germany, Austria, Finland and Czech Republic in healthy infants between March 2008 and January 2010. Three injections of rMenB+OMV NZ were administered intramuscularly (IM) at 2, 4 and 6 months of age. The study assessed the immunogenicity and safety of rMenB+OMV NZ and the consistency of the antibody response to3 consecutively produced lots of rMenB+OMV NZ. The study was also designed to demonstrate that the immunogenicity and safety of routine infant vaccines (i.e., combined DTaP-IPV-HBV-Hib vaccine and pneumococcal conjugate vaccine) when given concomitantly with Novartis rMenB+OMV NZ at 2, 4 and 6 months of age was noninferior to that of routine infants vaccines given without rMenB+OMV NZ. A total of 3630 subjects were enrolled (3600 were planned). Subjects were followed up for 6 months after the last (primary series) vaccination.

Primary objective: Immunogenicity:

- 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.

Secondary objectives:

- To assess the consistency of immune response from 3 lots of rMenB+OMV NZ, as measured by percentage of subjects with hSBA titre ≥ 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.

Safety:

- To assess the safety and tolerability of 3 doses of rMenB+OMV NZ when given concomitantly with routine infant vaccines at 2, 4 and 6 months of age (i.e., combined DTPa- HBV-IPV/Hib1 vaccine and pneumococcal conjugate vaccine).

7.1.1.1.2. Inclusion and exclusion criteria

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.

Inclusion criteria

Subjects were eligible to be enrolled in the study if they complied with the following criteria:

- Healthy 2-month-old infants (55-89 days, inclusive), born after full term pregnancy with an estimated gestational age ≥37 weeks and birth weight ≥2.5 kg;
- A parent/legal guardian has given written informed consent after the nature of the study has been explained;
- Available for all the visits scheduled in the study;
- In good health as determined by the investigator.

Exclusion criteria

Individuals were not eligible to be enrolled into this study if they had:

- A history of any meningococcal B vaccine administration;

- Prior vaccination with any Diphtheria, Tetanus, Pertussis (acellular or whole cell), Polio (either Inactivated or Oral), *Haemophilus influenzae* type b (Hib), and Pneumococcal antigens;
- Previous ascertained or suspected disease caused by *N meningitidis*;
- Household contact with and/or intimate exposure to an individual with laboratory-confirmed *N meningitidis*;
- History of severe allergic reaction after previous vaccinations or hypersensitivity to any vaccine component;
- Significant acute or chronic infection within the previous 7 days or rectal temperature ≥38°C within the previous day;
- Antibiotics within 6 days prior to enrolment;
- Any serious chronic or progressive disease according to the judgment of the investigator (e.g., neoplasm, diabetes mellitus Type I, cardiac disease, hepatic disease, progressive neurological disease or seizure, either associated with fever or as part of an underlying neurological disorder or syndrome, autoimmune disease, HIV infection or AIDS, or blood dyscrasias or diathesis, signs of cardiac or renal failure or severe malnutrition);
- Known or suspected impairment/alteration of the immune system, immunosuppressive therapy, use of systemic corticosteroids or chronic use of inhaled high-potency corticosteroids since birth;
- Receipt of blood, blood products and/or plasma derivatives or any parenteral immunoglobulin preparation;
- Receipt of, or intent to immunize with any other vaccine(s) (with the exception of Rotavirus vaccines), within 30 days prior and throughout the study period;
- Participation in another clinical trial since birth or planned for during study;
- Family members and household members of research staff;
- Any condition which, in the opinion of the investigator, might interfere with the evaluation of the study objectives.

7.1.1.1.3. Study treatments

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. The test vaccine, rMenB+OMV NZ (or Menjugate in the MenC+Routine group) was administered IM into the antero-lateral area of the right thigh, and both Infanrix Hexa and Prevenar were administered IM into the antero-lateral area of the left thigh. In the Routine group, Infanrix Hexa and Prevenar were administered in different legs. Menjugate (meningococcal C conjugate vaccine), for the MenC+Routine group only, was considered as a reference vaccine. Menjugate was administered (0.5 mL IM) into the antero-lateral area of the right thigh. The lyophilized MenC component of Menjugate was re-suspended with the saline solvent (aluminium hydroxide suspension) supplied with the Menjugate Kit, just before injection. After reconstitution Novartis Menjugate contains 10 µg MenC oligosaccharide conjugated with 12.5-25.0 µg CRM197.

7.1.1.1.4. Efficacy variables and outcomes

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 (% ≥1:5, i.e. 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 44/76, 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 titres % ≥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 the Table 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 specified in the Table below for that antigen {PConcomitant Vaccine +rMenB+OMV NZ minus PConcomitant 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.

Table 15: Concomitant Vaccine Antigen Test Type and Response End-Points Vaccine Test Antigens Cut-off level

Vaccine	Test	Antigens	Cut-off level
InfanrixHexa	ELISA	Diphtheria (D)	≥0.1 IU/mL and ≥1.0 IU/mL
	ELISA	Tetanus (T)	≥ 0.1 IU/mL and ≥ 1.0 IU/mL
	ELISA	PT (aP) FHA Pertactin	Seroconversion defined as either 1) a 4-fold increase for each pertussis antigen in those subjects seronegative at baseline or 2) in those initially seropositive, persistence of the pre-vaccination antibody concentration at least at the same antibody concentration as before vaccination, taking into account the decay of maternal antibodies.
	NT	Polio type 1 Polio type 2 Polio type 3	≥ 1:8
	ELISA	Hep B (HBV)	≥ 10 mIU/mL
	ELISA	PRP-T Hib	≥ 0.15 µg/mL and ≥ 1.0 µg/mL

7.1.1.1.5. Randomisation and blinding methods

The study consisted of two parts:

Part 1: Subjects in the randomized, open-label group were evaluated for the safety and immunogenicity of rMenB+OMV NZ when given concomitantly with routine infant vaccines. A blinded lot-to-lot consistency evaluation was embedded in this part of the study. Control subjects received routine vaccines only.

Part 2: Subjects in the randomized, observer-blind group were evaluated for safety only. The control subjects received Menjugate plus routine infant vaccines. The purpose of the study was to minimize bias in the assessment of safety.

Subjects meeting the enrolment criteria were assigned to one of five vaccination groups (ratio 4:4:4:3:3). 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 enrolled in Finland (safety subset), Austria, Germany and Italy (approx. 1200 subjects planned) were evaluated for safety only and formed the observer-blind subset (each subject's parents or caretakers, as well as the investigators evaluating the subject were blinded as to whether the subject received rMenB+OMV NZ or Menjugate). Subjects were randomized in a 1:1:1:3 ratio to the rMenB lot1 group, the rMenB lot2 group, the rMenB lot3 group or the MenC+Routine group.

Blood samples were obtained for serology testing from subjects in the open-label immunogenicity subset at baseline, and one month after the third vaccination visit. No blood draws were performed in the observer-blind (safety only) subset. Local and systemic reactions, daily body temperature, fever (defined as rectal temperatures ≥38.5°C), and antipyretic use were collected from days 1 to 7 after each vaccination. Other AEs, AEs leading to premature withdrawal, SAEs and medically attended AEs, including medically attended fever, were also collected from days 1 to 7. Fevers, reactions persisting beyond day 7, medically attended AEs, AEs leading to premature withdrawal, SAEs, all medications for treating reported AEs, and

vaccinations other than with the study vaccines were collected from day 8 after each vaccination to next vaccination or to 30 days after last vaccination. Medically attended AEs, AEs leading to premature withdrawal, SAEs, all medications for treating reported AEs, and vaccinations other than with the study vaccines were collected from 31 days after last vaccination to the last visit (end of study).

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.

7.1.1.1.6. Analysis populations

These definitions of populations analysed apply to all studies in this application:

(a) All enrolled population:

· all subjects who are enrolled in this study irrespective of whether they have been randomized or not. [There were no analyses based on the "All Enrolled Population"].

(b) Full Analysis Set/Modified Intention-to-treat (MITT) population, Immunogenicity:

· all subjects in the enrolled population who:
  – actually received a study vaccination, and
  – provided at least one evaluable serum sample after baseline

In case of randomization errors, subjects were to be analysed as randomized in the ITT analysis.

(c) Per protocol (PP) population, Immunogenicity:

· all subjects in the Full Analysis Set/MITT population who:
  – received all the relevant doses of vaccine correctly, and
  – provided evaluable serum samples at the relevant time points, and
  – had no major protocol violation as defined prior to analysis

A major deviation is defined as a protocol deviation that is considered to have a significant impact on the immunogenicity result of the subject (see below). In case of randomization errors, subjects were excluded from the PP analysis.

(d) Exposed population:

· all enrolled subjects who actually received a study vaccination

(e) Safety population:

· all subjects enrolled who:
  – have received study vaccination
  – provided post-baseline safety data

Major deviations:

· Subjects outside age window at Visit 1 (55 to 89 days, inclusive)
· Subjects randomized who did not meet study entry criteria
· Subjects who did not receive all study vaccinations (i.e., rMenB+OMV or Menjugate and/or concomitant vaccination)
· Subjects who did not have a blood draw after vaccination
· Subjects who developed withdrawal criteria during the study but were not withdrawn

- Subjects who received any prohibited concomitant medication. [Prohibited concomitant medications will be decided on a case-by-case basis prior to unblinding.]
- Subjects outside immunization window as defined as follows:

  Subjects should have 3 doses of rMenB+OMV NZ or Menjugate and/or InfanrixHexa and Prevenar, at least 30 days apart and dose 3 not be given at age ≥ 270 days (~ 9 months of age). Subjects not meeting all three criteria will be considered to have a major protocol deviation
- Subjects outside blood draw window as defined as follows: post-vaccination blood draw must be within 23 to 55 days post vaccination 3.

7.1.1.1.7. Sample size

The necessary sample size was calculated according to the following predictions: With 350 evaluable subjects per lot assayed for strains 44/76, 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 would be >99%, >99%, 98% for 44/76, 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 98%. The power of the 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%. Table 16 shows the number enrolled in each group.

Table 16: Numbers of Subjects Planned for Evaluation, and Evaluated

	rMenB lot1	rMenB lot2	rMenB lot3	rMenB All	Routine	MenC +Routine	Total
	N=833	N=828	N=820	N=2481	N=659	N=490	N=3630
Population:							
Planned	800	800	800	2400	600	600	3600
Enrolled	833 (100%)	828 (100%)	820 (100%)	2481 (100%)	659 (100%)	490 (100%)	3630 (100%)
Vaccinated	832 (100%)	828 (100%)	820 (100%)	2480 (100%)	659 (100%)	490 (100%)	3629 (100%)
Immunogen-icity hSBA (PP)	388 (47%)	381 (46%)	391 (48%)	1160 (47%)	122 (19%)	0	1282 (35%)
Safety	832 (100%)	828 (100%)	820 (100%)	2480 (100%)	659 (100%)	490 (100%)	3629 (100%)
Safety Open Label	661 (79%)	654 (79%)	652 (80%)	1967 (79%)	659 (100%)	0	2626 (72%)
Safety Observer Blind	164 (20%)	168 (20%)	161 (20%)	493 (20%)	0	470 (96%)	963 (27%)

7.1.1.1.8. Statistical methods

Table 17 and Table 18 summarise the specified statistical criteria and terms used for evaluating immunogenicity endpoints in all the studies presented in the efficacy data. Table 17 focuses on the immunogenicity assessment of rMenB+OMV NZ, while Table 18 focuses on the immunogenicity of the routine vaccine antigens.

Primary

For the three rMenB+OMV NZ lots, GMTs and 95% CI were calculated by exponentiating (base 10) the least squares means and the lower and upper limits of the 95% CIs of the log transformed titres (base10) obtained from a two-way Analysis of Variance (ANOVA) with factors for vaccine lot and study centre. 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 titres and the lower and upper limits of the 95% CIs on the difference obtained from the ANOVA model above. For the three rMenB+OMV NZ lots combined, percentages of subjects with hSBA titres ≥1:5 and associated 95% CIs were computed for each strain.

Secondary

For the routine group Unadjusted GMTs and 95% CIs were calculated. For the three rMenB+OMV lots, the percentage of subjects with hSBA titer ≥ 1:5 prior to the first and at 1 month after the third vaccination and the associated 95% CIs were computed for each strain. Lot-to-lot differences in these percentages and associated 95% CIs were computed for each pair of rMenB+OMV lots using the Miettinen and Nurminen method. The percentage of subjects with hSBA titer ≥ 1:8 and fourfold rise in titer at 1 month after the third vaccination over the pre-vaccination titer and the associated 95% CIs were also calculated by Meningococcal B strain.

For the three vaccine lots, Geometric Mean Concentrations (GMCs) against vaccine antigen 287-953 were calculated. GMCs and 95% CI were calculated by exponentiating (base 10) the least squares means and the lower and upper limits of the 95% CIs of the log transformed concentrations (base10) obtained from a two-way Analysis of Variance (ANOVA) with factors for vaccine lot and study centre. For the routine vaccination group unadjusted ELISA GMCs were calculated. 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 and 95% CI, at one month following the third vaccination were calculated. The immune response to Polio type 1, type 2, and type 3 vaccine was measured by neutralization test (NT). The GMCs for antigens against routine vaccinations and 95% CIs were constructed by exponentiating (base 10) the least squares means of the logarithmically transformed (base 10) titres and their associated 95% CIs obtained from a one-way Analysis of Variance (ANOVA) with a factor for vaccine group (3 lots combined vs Routine). Titres below the limit of detection were set to half the limit of detection for the purpose of analysis. Additionally, median, minimal, and maximal titres (or concentrations) were calculated.

Table 17: Statistical Criteria for Evaluating the Immunogenicity of rMenB+OMV NZ

Study	Key Analysis	Endpoints	Objective	Statistical Criteria For Evaluating Each Endpoint
V72P12	Sufficient immune response at 1 month after third vaccination.	≥1:5	Primary	For group 1 (rMenB+OMV NZ with concomitant vaccines at 2, 4, 6 months of age) and group 3 (rMenB+OMV NZ with concomitant vaccines at 2, 3, 4 months of age): lower limit of the 2-sided 95% CI for the percentages of subjects with hSBA ≥ 1:5 is equal to or greater than 70% for strains 44/76, NZ98/254 and 5/99.
	Non-inferiority when given concomitantly with routine infant vaccinations	≥1:5	Secondary	Non-inferiority is shown if 2-sided 95% lower confidence interval of the difference between group 1 (one dose of rMenB+OMV NZ at 2, 4, and 6 months of age, administered concomitantly with routine infant vaccinations) and 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) at 30 days after the last rMenB+OMV NZ vaccination is greater than -10% for each of the 3 strains tested.
V72P13	Lot-to-lot consistency	GMT	Co-Primary	Immunogenicity of the 3 lots of rMenB+OMV NZ are considered equivalent if for each of the 3 strains and each pair of vaccine lots, the 2-sided 95% CI on the ratio of GMTs at 1 month after third vaccination is contained within the interval [0.5, 2.00]
	Sufficient immune response at 1 month after third vaccination.	≥1:5	Co-Primary	Lower limit of the 2-sided 95% CI for the percentage of subjects with hSBA ≥1:5 for the three lots combined is equal to or greater than 70% for each of the three reference strains 44/76, NZ98/254 and 5/99.
	Lot-to-lot consistency	≥1:5	Secondary	For each of the three strains and each pair of vaccine lots, the 95% CIs on the differences at 1 month after the third dose, is entirely within the interval [-10%, 10%].
V72P13E1	Sufficient immune response 1 month after booster, with or without MMRV	≥1:5	Primary	Lower limit of the 2-sided 95% CI for the percentage of subjects with hSBA titer ≥ 1:5 one month after the fourth dose is equal to or greater than 75% for each of the three serogroup B reference strains
	Immunological memory induction	GMT	Secondary	Lower limit of the 2-sided 95% CI for the ratio of the hSBA GMTs following a fourth dose of rMenB+OMV NZ at 12 months of age compared to the hSBA GMTs following a single dose of rMenB+OMV NZ at 12 months of age (GMT Post-dose 4 / GMT Post-dose 1) is equal to or greater than 2.0.
Study	**Key Analysis**	**Endpoints**	**Objective**	**Statistical Criteria For Evaluating Each Endpoint**
V72P13E2	Antibody persistence	≥1:5, GMT	Primary	No criterion specified
	Response to booster dose	≥1:5, GMT	Secondary	No criterion specified

Table 18: Statistical Criteria for Evaluating Immunogenicity of Routine Infant Vaccinations Given With and Without rMenB+OMV NZ

Study	Focus of Analysis	Endpoints	Objective	Statistical Criteria For Evaluating Each Endpoint
V72P12	Non-inferiority (Infanrix Hexa, Prevenar)	For ELISA, NT cutoffs see Table 1-1b above	Secondary	To demonstrate non-inferiority of antibody responses to routine vaccines (Infanrix Hexa, Prevenar) when given concomitantly with 3 doses of rMenB+OMV NZ administered at 2, 3, and 4 months of age vs. when given alone: the lower limit of the 2-sided 95% CI for the difference in the percentage of subjects with antibody response greater than or equal to the cut-off level specified in Table 1-1b for that antigen {$P_{\text{Concomitant Vaccine +rMenB+OMV NZ}}$ minus $P_{\text{Concomitant Vaccine}}$} is greater than -10%.,
	Non-inferiority (Pertussis components of Infanrix Hexa)	For pertussis GMCs see Table 1-1b above	Secondary (additional analysis)	Lower limit of the 2-sided 95% CI for the ratio of GMCs ($GMC_{\text{rMenB+OMV NZ+InfanrixHexa}}$ / $GMC_{\text{InfanrixHexa}}$) is equal to or greater than 0.67 after vaccinations at 2, 3, and 4 months of age.
V72P13	Non-inferiority (Infanrix Hexa, Prevenar)	For ELISA, NT cutoffs see Table 1-1b above	Secondary	To demonstrate non-inferiority of antibody responses to routine vaccines (Infanrix Hexa, Prevenar) when given concomitantly with 3 doses of rMenB+OMV NZ administered at 2, 4, and 6 months of age vs. when given alone: the lower limit of the 2-sided 95% CI for the difference in the percentage of subjects with antibody response greater than or equal to the cut-off level specified in Table 1-1b above for that antigen {$P_{\text{Concomitant Vaccine +rMenB+OMV NZ}}$ minus $P_{\text{Concomitant Vaccine}}$} is greater than -10%.
	Non-inferiority (Pertussis components of Infanrix Hexa)	For pertussis GMCs see Table 1-1b above	Secondary (additional analysis)	Lower limit of the 2-sided 95% CI for the ratio of GMCs ($GMC_{\text{rMenB+OMV NZ+InfanrixHexa}}$ / $GMC_{\text{InfanrixHexa}}$) is equal to or greater than 0.67 after vaccinations at 2, 4, and 6 months of age.
V72P13E1	Non- inferiority (MMRV)	For ELISA cutoffs see Table 1-1b above	Secondary	Lower limit of the 2-sided 95% CI for the difference in the percentage of subjects with antibody response {P_{MMRV} + rMenB+OMV NZ minus P_{MMRV}} is greater than -10%.

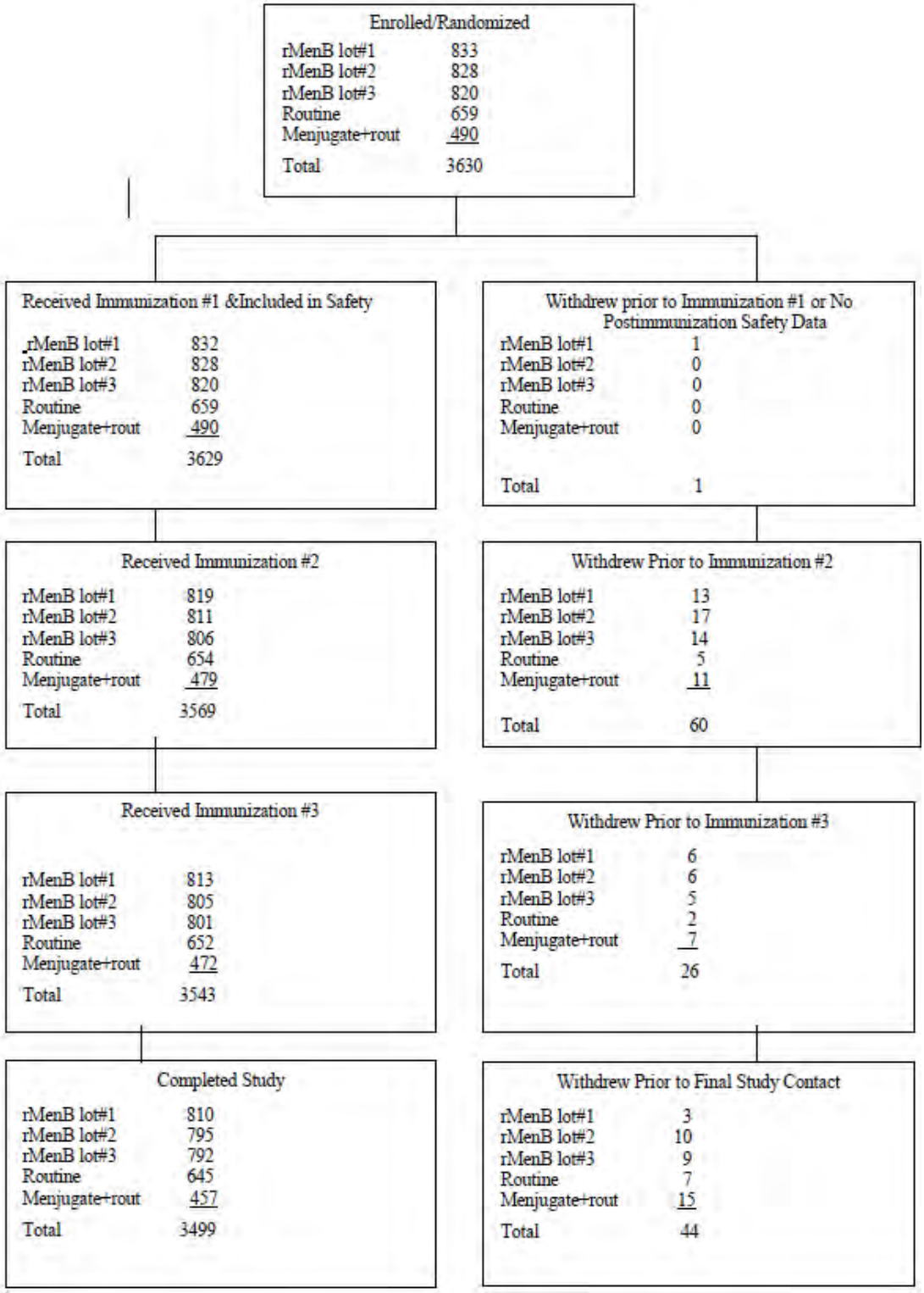
7.1.1.1.9. Participant flow

Table 19 and Figure 6 show the participant flow through this study.

Table 19: Total enrolled participants in V72P13

Vaccine Group	rMenB lot1	rMenB lot2	rMenB lot3	Routine	MenC+Routine
Enrolled	833	828	820	659	490
Completed study	810 (97%)	795 (96%)	792 (97%)	645 (98%)	457 (93%)
Premature withdrawals					
AE	7 (<1%)	7 (<1%)	6 (<1%)	7 (<1%)	1 (1%)
Withdrew consent	7 (<1%)	15 (2%)	15 (2%)	5 (<1%)	9 (2%)
Lost to follow-up	9 (1%)	9 (1%)	7 (<1%)	1 (<1%)	21 (4%)
Protocol deviation	0	2 (<1%)	0	1 (<1%)	2 (<1%)

Figure 6: Participant flow through study V72P13



7.1.1.1.10. Major protocol violations/deviations

Major protocol deviations were reported for 319 subjects, while minor protocol deviations were reported for 1190 subjects (Table 20). Major deviations were mostly due to missing blood draws, subjects not completing the vaccination course, and subjects receiving an incorrect vaccine. All subjects with major protocol deviations (except those with missing blood draws at

visit 1 for those routine antigen assessments that did not require baseline values, such as HBV) were excluded from the immunogenicity analysis but were analysed for safety.

Table 20: Number (%) of Subjects with Protocol Deviations

Reasons	rMenB lot1	rMenB lot2	rMenB lot3	Routine	MenC+Rout
	N=833	N=828	N=820	N=659	N=490
Major deviations:	77(9%)	86(10%)	60(7%)	52(8%)	44(9%)
3rd Vaccination Outside Age Time Window	1(<1%)	2(<1%)	1(<1%)	3(<1%)	0
3rd Vaccination Outside Time Window	0	1(<1%)	0	0	0
Blood Draw Outside Window Visit	6(<1%)	5(<1%)	5(<1%)	7(1%)	0
Did Not Meet Entry Criteria	3(<1%)	7(<1%)	6(<1%)	6(<1%)	1(<1%)
Incorrect Vaccine/Wrong Dose Given	6(<1%)	5(<1%)	4(<1%)	5(<1%)	1(<1%)
No Full Vaccination Course	23(3%)	27(3%)	24(3%)	7(1%)	26(5%)
No Vaccination Received	1(<1%)	0	0	0	0
Outside Age Window	1(<1%)	0	1(<1%)	0	0
Received Excluded Concomitant Medication	0	0	1(<1%)	1(<1%)	0
Subject Did Not Provide Visit 1 Blood Draw	28(3%)	26(3%)	15(2%)	19(3%)	n/a
Subject Did Not Provide Visit 4 Blood Draw	10(1%)	11(1%)	4(<1%)	7(1%)	n/a
Unblinding Issue	7(<1%)	6(<1%)	7(<1%)	0	20(4%)

Subjects may be included in more than one category

7.1.1.1.11. Baseline data

The demographic and other baseline characteristics were balanced across the different vaccination groups. The majority of the immunogenicity subjects were Caucasian (99% to 100%). Subjects for the open-label immunogenicity subset (N=1282) of this study were enrolled in the Czech Republic and Finland. They were randomized in a 1:1:1:1 ratio to the rMenB+OMV NZ lot1 group, the rMenB+OMV NZ lot2 group, the rMenB+OMV NZ lot3 group, or to a Routine vaccinations only group. Blood samples were obtained for serology testing from these subjects at baseline, and one month after the third vaccination visit.

7.1.1.1.12. Results for the primary efficacy outcome

Study immunogenicity results

The primary immunogenicity objectives of the study were met. The first co-primary objective was to establish lot-to-lot consistency. Antibody responses to the 3 lots of rMenB+OMV NZ vaccine were consistent from lot to lot. The pre-specified statistical criterion for demonstration of consistency was met in that the 95% CI on the ratios of the GMTs of bactericidal antibody against each of the three reference strains after the third vaccination for lot 1 vs. lot 2, lot 2 vs. lot 3, and lot 1 vs. lot 3 were, [0.78, 1.27], entirely contained within the interval of [0.5, 2.00].

A secondary objective was to evaluate the consistency of the immune response across the 3 manufacturing lots based on the percentage of subjects achieving hSBA ≥1:5 at one month after the third vaccination, against each of the three reference strains. The immune responses of the three vaccine lots were considered equivalent as they met the prespecified criterion: for each of

the three reference strains and each pair of vaccine lots, the two-sided 95% CIs of the differences in the percentage of subjects with hSBA ≥ 1:5 at 1 month after the third dose, were all entirely within the interval [-10%, 10%]. The lowest bound observed was -9% and the highest bound was 8%, both for strain NZ98/254.

The second co-primary objective was also met in that antibody responses against the three reference strains were sufficient. The lower limit of the two-sided 95% CI for the percentage of subjects with hSBA ≥ 1:5 at 1 month following the third vaccination was ≥ 70% for all strains for the three lots combined. Responses were 100% against the 44/76 and 5/99 strains and 84% against the NZ98/254 strain. The results of this study showed that rMenB+OMV NZ may be administered concomitantly with routine paediatric vaccines. The rMenB+OMV NZ vaccination did not interfere with the immune response to the diphtheria, tetanus, pertussis, HBV, poliovirus types 1 and 3, or PRP-Hib, antigens contained in Infanrix Hexa or the 7 pneumococcal antigens contained in Prevenar.

Pre-specified statistical criteria for demonstration of non-inferiority of the antibody responses to routine vaccines when administered with rMenB+OMVNZ as compared to when the vaccines were given alone were met for all responses evaluated with the exception of the response for poliovirus antigen type 2 in Infanrix Hexa. For the pertussis components, non-inferiority was also evaluated based on the ratio of GMCs to the three pertussis antigens (PT, FHA, pertactin).

The ratio of the GMC of antibody responses to these antigens after vaccinations at 2, 4, and 6 months of age for infants who received rMenB+OMV NZ+Infanrix Hexa as compared with the responses for infants who received Infanrix Hexa alone was ≥0.67. The point estimates for tetanus, HBV, Hib, pertussis, and IPV GMCs/GMTs appeared to be lower in the subjects receiving rMenB+OMV NZ concomitantly with Infanrix Hexa and Prevenar as compared to the subjects receiving these routine vaccinations alone. The ratio of GMCs for (rMenB+routine: Routine) for these antigens ranged from 0.6 to 0.84.

Overall, there was a robust bactericidal immune response against all 3 reference strains observed after vaccination with rMenB+OMV NZ in this large population of infants. The results support the use of this candidate vaccine in a 3-dose schedule co-administered with routine infant vaccinations for protection against meningococcal disease caused by serogroup B.

7.1.1.1.13. Results for other efficacy outcomes

There was no evidence from the primary analysis specified in this study for the secondary objective that rMenB+OMV NZ vaccination interfered with the immune response to the diphtheria, tetanus, pertussis (pertussis toxin, FHA, pertactin), HBV, polio types 1 and 3, or Hib antigens contained in Infanrix Hexa or the 7 pneumococcal antigens contained in Prevenar. Non-inferiority criteria were not met, however, for polio type 2. For the pertussis component, InfanrixHexa given concomitantly with rMenB+OMV NZ was also found to be non-inferior to that of InfanrixHexa alone based on the ratio of GMCs (GMC rMenB+OMV NZ + InfanrixHexa/GMC InfanrixHexa was ≥0.67 after vaccination at 2, 4, and 6 months of age). Non-inferiority was further demonstrated for FHA and PT pertussis antigens in terms of percentage of subjects with fourfold increase in antibody response (an additional, more conservative analysis). The lower limit of the interval for the pertactin component was -16% and so non-inferiority could not be shown by this analysis. There was a trend towards lower tetanus, HBV, Hib, pertussis, and IPV GMCs/GMTs in the subjects receiving rMenB+OMV NZ concomitantly with Infanrix Hexa and Prevenar as compared to the subjects receiving these routine vaccinations alone. The ratio of GMCs for (rMenB+routine: Routine) for these antigens ranged from 0.6 to 0.84.

> **Comment:** This is the largest study contained in this application and, importantly, involves the infant target group. The information from this study (both efficacy and safety) is pivotal for this age group. It is conducted in a number of countries. It appears to be well conducted and has two follow-on studies. It terms of efficacy, it shows robust immunogenicity in all

groups as well as flexibility in administration schedules and ability to co-administer rMenB+OMV NZ with other childhood vaccinations.

7.1.1.2. Study V72P10

7.1.1.2.1. Study design, objectives, locations and dates

V72P10 was a phase 2b/3, observer-blind, multi-centre, randomized, controlled study conducted in Chile in healthy adolescents 11 to 17 years of age, from June 2008-April 2010. The vaccine was administered according to a 1 dose, 2 dose or 3 dose vaccination schedule, to evaluate the optimal vaccination schedule in an adolescent population. The multidose schedules investigated were 2 doses given 1, 2 or 6 months apart, 3 doses given one month apart, or 3 doses given at months 0, 1 and 6 or months 0, 2 and 6 as shown in Table 21.

Table 21: Overview of Vaccine Groups in Study V72P10

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

The main aim of the study was to assess the antibody response and short-term persistence and safety after one, two, or three injections of rMenB+OMV NZ in healthy adolescents in various vaccination schedules. Blood samples (approximately 15 mL) were obtained for meningococcal serology from all subjects at baseline, 1 month after first, second and third vaccinations. The blood samples were also obtained 1 month after an additional vaccine dose administered at Month-6. Sera collected were assayed to assess the immune response to the rMenB+OMV NZ vaccines administered, by evaluation of the serum bactericidal activity using human complement (hSBA).

7.1.1.2.2. Inclusion and exclusion criteria

Inclusion criteria

Individuals eligible to be enrolled into this study were male and female subjects:

- 11-17 years of age inclusive who have given their written assent and whose parents or legal guardians have given written informed consent at the time of enrolment;
- who are available for all the visits scheduled in the study (i.e., not planning to leave the area before the end of the study period);
- in good health as determined by the outcome of medical history, physical examination and clinical judgment of the investigator.

Exclusion criteria

Individuals not eligible to be enrolled into this study are those who:

- History of any meningococcal B vaccine administration;
- Current or previous, confirmed or suspected disease caused by *N. meningitidis*;
- Household contact with and/or intimate exposure to an individual with any laboratory confirmed *N. meningitidis* infection within 60 days of enrolment;
- Significant acute or chronic infection within the previous 7 days or fever (defined as axillary temperature ≥38°C) within the previous day;
- Antibiotics within 6 days prior to enrolment;
- Pregnancy or nursing (breastfeeding) mothers;
- Females of childbearing age who have not used or do not plan to use acceptable birth control measures, for the 7 months duration of the study. Oral, injected or implanted hormonal contraceptive, diaphragm, condom, intrauterine device or sexual abstinence are considered acceptable forms of birth control. If sexually active the subject must have been using one of the accepted birth control methods at least two months prior to study entry;
- Any serious chronic or progressive disease (e.g., neoplasm, diabetes, cardiac disease, hepatic disease, progressive neurological disease or seizure disorder; autoimmune disease, HIV infection or AIDS, or blood dyscrasias or diathesis, signs of cardiac or renal failure or severe malnutrition);
- Known or suspected impairment/alteration of the immune system, immunosuppressive therapy, including use of corticosteroids in immunosuppressive doses or chronic use of inhaled high-potency corticosteroids within the previous 60 days. [Use of topical corticosteroids administered during the study in limited areas (i.e., eczema on knees or face or elbows) of the body is allowed]; immunostimulants;
- Receipt of blood, blood products and/or plasma derivatives, or a parenteral immunoglobulin preparation within the previous 90 days;
- History of severe allergic reactions after previous vaccinations or hypersensitivity to any vaccine component;
- Receipt of or intent to immunize with any other vaccine(s) within 30 days prior (60 days for live viral vaccines) and throughout the study period (exception: licensed flu vaccine should not be administered within 14 days prior to enrolment; routine vaccine may be administered after the blood draw at study month 7);
- Participation in another clinical trial within last 90 days or planned for during study;
- Family members and household members of research staff;
- Any condition which in the opinion of the investigators may interfere with the evaluation of the study objectives.

7.1.1.2.3. Study treatments

Vaccine or placebo was administered. A total of 4 injections at months 0, 1, 2 and 6 were administered to each subject, rMenB+OMV NZ was administered as one dose of 0.5 mL at month 0 or month 6; or two doses at months 0 and 1, or at months 0 and 2, or at months 0 and 6; or three doses at months 0, 1, and 2, or at months 0, 1 and 6, or at months 0, 2 and 6. Placebos were given when rMenB+OMV NZ was not administered. A control group received three injections of placebo.

7.1.1.2.4. Efficacy variables and outcomes

The primary efficacy outcome was to precisely estimate the percentage of subjects with hSBA ≥1:4 at month 1, month 2 and month 3 for the different vaccination schedules. Secondary objectives included geometric mean titres (GMTs). Additionally, the hSBA data for all the above-mentioned criteria were also analysed stratified by pre-vaccination titer (i.e. hSBA titer <1:4 and ≥1:4).

7.1.1.2.5. Randomisation and blinding methods

Subjects meeting enrolment criteria were randomized in an observer-blind manner to 8 groups (Groups 1a, 1b, 2a, 2b, 3a, 3b, 4 and 5) in approximately 1:2:1:2:1:2:3:1 ratio stratified by age groups of 11 to 13 years and 14 to 17 years. The Groups 1a and 1b, 2a and 2b, and 3a and 3b differed in the vaccination schedule after Visit-4 (Month-3). Subjects were randomly assigned in a 1:2:1:2:1:2:3:1 ratio to one of the vaccination groups. 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.

Because the presentation of the two study vaccines was 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, and were instructed not to reveal the identity of the study vaccines neither to the subject 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 study monitor was notified by the investigator. Study vaccine codes were not freely available to the investigator or personnel monitoring the trial until after the completion of the trial and final data review.

7.1.1.2.6. Analysis populations

A total of 1631 subjects were enrolled and randomized to 8 groups stratified by age group (11 to 13 and 14 to 17 years of age). The total numbers receiving each different regimen are summarised in Table 22.

Table 22: Overview of Subjects Planned and Analysed

	rMenB0	rMenB01	rMenB02	rMenB012	Placebo	Total
Planned (N)	375	375	375	375	125	1625
Enrolled (N)	375	375	380	373	128	1631
MITT [N (%)]	337 (90%)	345 (92%)	342 (90%)	335 (90%)	116 (91%)	1475 (90%)
PP Population [N (%)]	336 (90%)	330 (88%)	320 (84%)	304 (82%)	108 (84%)	1398 (86%)
Safety Population [N (%)]	375 (100%)	375 (100%)	380 (100%)	373 (100%)	128 (100%)	1631 (100%)

7.1.1.2.7. Sample size

Calculations were based on previous percentage of vaccine responders. To appropriately power the study, it was calculated that 300 participants would be needed in each group. To obtain 1300 evaluable subjects it was estimated that approximately 1625 eligible subjects were to be enrolled, to allow for a 20% drop out rate. These subjects were randomly assigned to one of the eight vaccination groups (in a ratio of 1:2:1:2:1:2:3:1).

7.1.1.2.8. Statistical methods

The statistical evaluation of the results was performed by BCDM and statistical tables and graphs were generated using SAS version 9.1 or higher. Baseline was defined as the time before receiving the first vaccination. Missing values were left out in the appropriate analyses because they were regarded as non-informative. The main analysis of the study was performed on:

- immunogenicity data from visit 1 to 4 (i.e. until one month after third injection)
- all safety data collected until visit 4

The follow-up analysis of the study will be performed on the following data:

- immunogenicity data and safety data on an additional dose, given at study month-6
- longer term safety data collected for six months after each subject's last administration of rMenB+OMV NZ or placebo

[**Information redacted**] The main immunogenicity population is the PP population. Immunogenicity analyses were to be performed on both the PP and MITT populations. For the immunogenicity endpoints calculated for the primary (Months-0, 1, 2 and 3) and the follow-up (Months-6 and 7) study periods for each meningococcal B strain are as follows:

- The percentage of subjects with hSBA titer ≥1:4 and ≥1:8, the point estimates along with the associated 95% confidence intervals (CIs) were to be tabulated.
- The percentage of subjects with at least a 4-fold rise in hSBA titer over the pre-vaccination titre, the point estimate and the associated 95% CIs were to be calculated.

For each meningococcal B strain for which hSBA was measured, the percentage of subjects with a titer ≥1:4, ≥1:8 and the percentage of subjects with a fourfold rise in titres are presented as point estimates along with the associated 95% CIs were given at all the stipulated time-points. After stratification of subjects based on baseline hSBA titres of <1:4/≥1:4, the percentage of subjects achieving post vaccination hSBA titres ≥1:4 along with the associated 95% CIs were computed by vaccine group, time point and meningococcal strain. Median, minimal, and maximal titres were calculated. All subjects receiving at least one injection and providing post-baseline safety data were included in the safety and tolerability analyses.

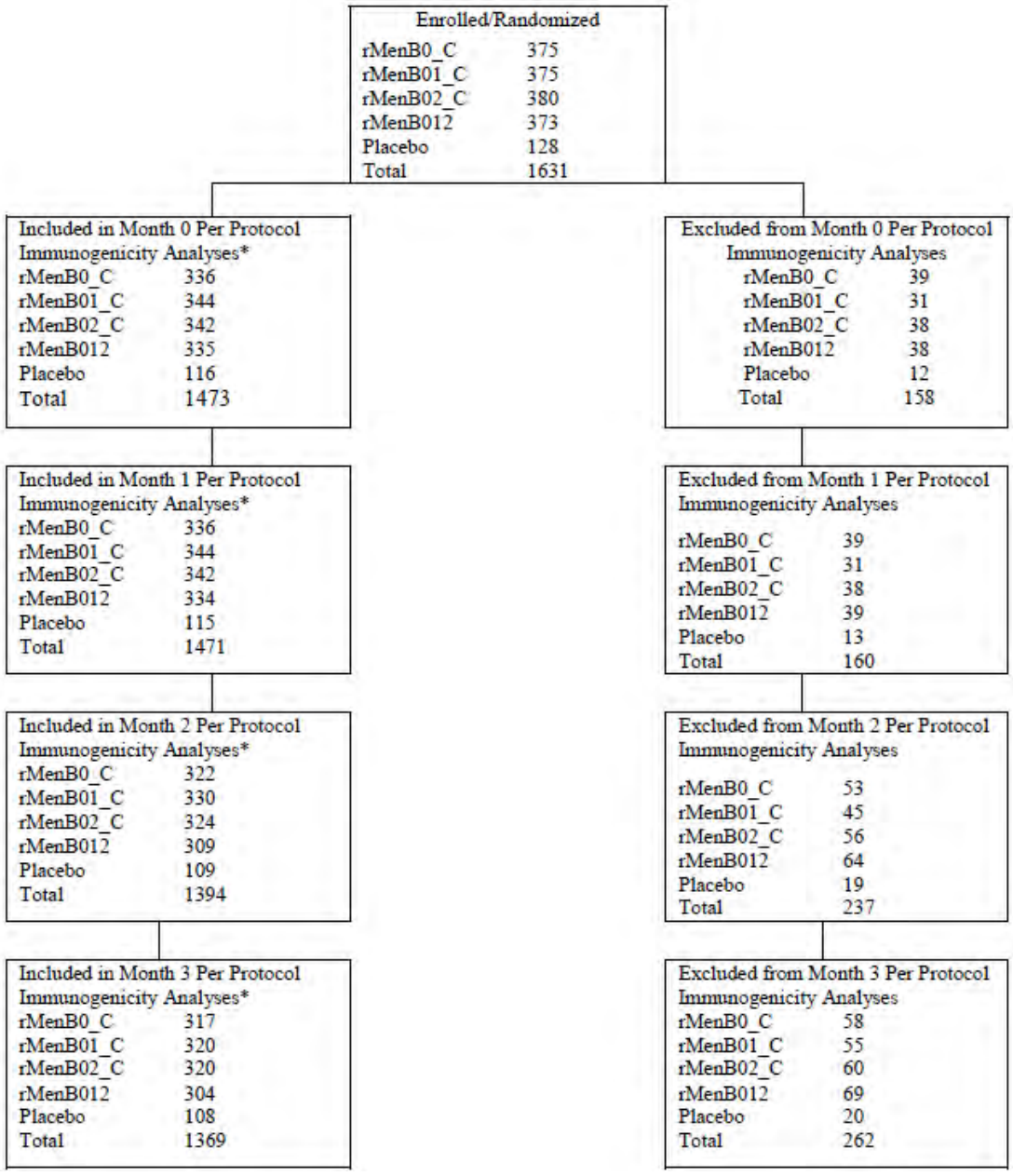
7.1.1.2.9. Participant flow

Overall, 1631 subjects were enrolled into the study and randomized into eight vaccine groups. Across the vaccine groups, 7% to 11% subjects were withdrawn from the study until visit-4, with the most common reason being withdrawal of consent; most of these subjects withdrew consent after the first visit. Other common reasons were subjects being lost to follow-up and protocol deviations (Table 23). The protocol deviations that lead to study termination were mostly due to errors in administration of the investigational vaccine and subjects testing positive for pregnancy. There was no considerable difference among the vaccine groups and Placebo in the percentage of pre-mature withdrawals. The flow through the Study is shown in Figure 7.

Table 23: Summary of Study Terminations in Subjects Aged 11 to 17 Years Up to Month-3 (Visit-4) - Enrolled Population

	rMenB0	rMenB01	rMenB02	rMenB012	Placebo
Enrolled (N)	375	375	380	373	128
Completed study until Visit-4 N (%)	342 (91%)	345 (92%)	341 (90%)	331 (89%)	119 (93%)
Premature withdrawals [a]	33 (9%)	30 (8%)	39 (10%)	42 (11%)	9 (7%)
Adverse event N (%)	1 (<1%)	0	0	0	0
Withdrew consent N (%)	27 (7%)	26 (7%)	33 (9%)	37 (10%)	8 (6%)
Lost to follow-up N (%)	3 (<1%)	1 (<1%)	5 (1%)	4 (1%)	0
Inappropriate Enrollment N (%)	0	0	0	1 (<1%)	0
Protocol Deviation N (%)	2 (<1%)	3 (<1%)	1 (<1%)	0	1 (<1%)

Figure 7: Subject Completion Flowchart V72P10- PP Population



7.1.1.2.10. Major protocol violations/deviations

Most commonly reported major protocol deviations were blood draw and vaccination performed out of the specified window of >14 days before first vaccination for first blood draw, -7/+14 days for second and third blood draws and vaccinations and -7/+25 for fourth blood draw. The deviations are summarised in Table 24.

Table 24: Protocol Deviations Up to Month-3 (Visit-4)- Enrolled Population

	rMenB0	rMenB01	rMenB02	rMenB012	Placebo
	N=375	N=375	N=380	N=373	N=128
Any Major Deviation	31 (8%)	28 (7%)	23 (6%)	31 (8%)	13 (10%)
1st BD Outside Window	0	1 (<1%)	0	0	0
2nd BD Outside Window (-7/+14 days)	14 (4%)	12 (3%)	5 (1%)	8 (2%)	9 (7%)
2nd Vacc. Outside Window(-7/+14 days)	13 (3%)	11 (3%)	5 (1%)	7 (2%)	8 (6%)
3rd BD Outside Window (-7/+14 days)	8 (2%)	10 (3%)	11 (3%)	16 (4%)	4 (3%)
3rd Vacc. Outside Window(-7/+14 days)	8 (2%)	10 (3%)	11 (3%)	15 (4%)	2 (2%)
4th BD Outside Window(-7/+25 days)	6 (2%)	7 (2%)	6 (2%)	6 (2%)	3 (2%)
Did Not Meet Entry Criteria	1 (<1%)	0	0	1 (<1%)	0
Outside Age Window	1 (<1%)	0	0	0	0
[a]Excluded Concomitant Medications	2 (<1%)	0	0	3 (<1%)	0
Wrong Vaccination	4 (1%)	2 (<1%)	1 (<1%)	0	0
No 3rd BD	1 (<1%)	0	2 (<1%)	0	0
No 4th BD	0	0	1 (<1%)	0	0
No 3rd Vacc	1 (<1%)	0	1 (<1%)	0	0
Any Minor Deviation	65 (17%)	66 (18%)	67 (18%)	62 (17%)	17 (13%)
1st BD Outside Window (≤14 days before enrollment)	13 (3%)	9 (2%)	12 (3%)	10 (3%)	2 (2%)
2nd BD Outside Window (-4/+7 days)	24 (6%)	26 (7%)	34 (9%)	24 (6%)	9 (7%)
2nd Vacc Outside Window (-4/+7 days)	24 (6%)	25 (7%)	30 (8%)	24 (6%)	9 (7%)
3rd BD Outside Window (-4/+7 days)	19 (5%)	16 (4%)	15 (4%)	13 (3%)	4 (3%)
3rd Vacc Outside Window (-4/+7 days)	19 (5%)	14 (4%)	14 (4%)	15 (4%)	4 (3%)
4th Vacc Outside Window(-4/+7 days)	15 (4%)	16 (4%)	16 (4%)	19 (5%)	5 (4%)
Diary Card Was Lost	2 (<1%)	1 (<1%)	0	0	0

7.1.1.2.11. Baseline data

The demographic and baseline characteristics of subjects including age, gender, ethnic origin, height and weight for the Per Protocol and MITT populations were balanced across the vaccine groups. Almost all the enrolled subjects met the study entry criteria. After exclusions, the PP population included 82% to 91% of the enrolled subjects in each vaccine group with no appreciable differences in the percentage of subjects included among the vaccine groups.

7.1.1.2.12. Results for the primary efficacy outcome

The most common reasons for exclusion from the PP population, included blood draw and vaccination performed out of the protocol-specified time window. After receiving one dose of rMenB+OMV NZ (N=1357), a large majority of subjects showed hSBA ≥1:4 (93% to 97% of subjects across the strains. A large proportion of subjects had a significant response to the vaccine with at least a 4-fold increase in titer from baseline (79% to 87% of subjects across the strains. There were 14 to 26-fold increases in the antibody titres (GMTs) across the strains. One month after the last dose of rMenB+OMV NZ across the vaccination schedules, almost all (99-100% across groups and strains) subjects who received two or three doses of rMenB+OMV NZ showed hSBA ≥1:4. In the group that received one dose of the vaccine, 92 to 97% of the subjects showed hSBA ≥1:4across the strains receiving 2 or 3 doses (rMenB01, rMenB02 and rMenB012) showed at least a 4-fold increase in hSBA titres from baseline one month after the last dose of test vaccine (92% to 99% across the groups and strains,. The response was lower in the group that received one dose (78% to 84% of subjects across the strains). Increases in GMTs were higher in subjects who received two or three doses of the rMenB+OMV NZ vaccine (55 to 62-fold against strain 44/76; 186 to 280-fold against strain 5/99; 29 to 44 fold against strain-NZ98/254) than in the subjects who received one dose of the test vaccine (13 to 24 fold across the strains), one month after receiving the last dose.

Overall, the immune response was higher in the groups receiving two or three doses of rMenB+OMV NZ. At the time-point of one month after receiving the last dose, there was no added antibody response in the subjects who received three doses as compared to the subjects who received two doses.

Between the groups administered two doses of vaccine with either an interval of one month (rMenB01) or two months (rMenB02) between doses, there was no clear difference in terms of percentage of subjects with hSBA ≥1:4 and ≥1:8 or in >4-fold increases in hSBA titres. There was a trend for the subjects receiving two doses, two months apart, to have higher GMTs across the three strains than the subjects administered two doses of vaccine, one month apart, particularly for strain 5/99. There was no clear or consistent advantage in antibody titres for the three-dose group (rMenB012) compared to the two-dose groups.

The subgroup analyses on the subjects with and without detectable hSBA titres at baseline showed that, regardless of the baseline status the subjects in all the vaccine groups showed a strong immune response. Subjects with hSBA <1:4 at baseline showed significant increases in GMTs and hSBA ≥1:4, one month after the last dose of rMenB+OMV NZ. Similarly, high hSBA responses were also observed in the subjects with baseline hSBA ≥1:4. The responses in both the subgroups were similar to the results obtained in the overall PP population.

7.1.1.2.13. Results for other efficacy outcomes

Secondary objectives in study V72P10 included an assessment of the immunogenicity of an additional dose of rMenB+OMV NZ given at month 6, by evaluation of the hSBA response at one month after the month 6 rMenB+OMV NZ dose, for schedules 0; 0, 1 and 0, 2, and an assessment of antibody persistence following various vaccination schedules of one, two (0, 1 or 0, 2 schedule) or three doses (0, 1, 2 schedule). All vaccine groups that received a booster vaccination with rMenB+OMV NZ at month 6 showed a robust antibody response in terms of percentage of subjects with hSBA≥1:4, 1:8 and GMTs/GMCs one month after the booster dose (at month-7). One month after booster dose, the rMenB06 vaccine group that received a single dose as primary vaccination (at month-0) followed by a booster dose (at month-6) showed a good immune response as almost all the subjects showed hSBA≥1:8 at month-7 and the great majority of subjects showed at least 4-fold increase in hSBA titres. There was no great difference between the one-dose and two-dose primary vaccine groups after the booster dose (rMenB06 versus rMenB016 and rMenB026), Indicating that a single dose of rMenB+OMV NZ vaccine was sufficient to induce immunological memory. Although not proposed originally,

these new data support a two dose primary vaccine schedule in adolescents with the two doses of rMenB+OMV NZ administered one to six months apart.

At four to six months after the primary vaccination course (at month-6), the persistence of the antibody response was substantially higher in the two-dose and three-dose primary vaccine groups (rMenB01, rMenB02 and rMenB012) than the one-dose primary vaccine group (rMenB0) in terms of percentage of subjects with hSBA≥1:4, and GMTs/GMCs. No substantial difference was noted among the two-dose and three-dose vaccine groups in terms of percentage of subjects with hSBA≥1:4, and ≥1:8. The GMTs at month-6 supported good persistence of the antibody response in the two-dose and three-dose vaccine groups as these titres were markedly higher than the original titres at baseline, as well as the titres of the placebo group at month-6 . Among the vaccine groups that did not receive a booster at month-6, all the two-dose and three-dose vaccine groups showed a higher persistence of the antibody response than the single-dose primary vaccine group at month-7. Consistent with the month-6 results, there was good persistence of the antibody response for the two-dose and three-dose vaccine groups; the rMenB01 group showed slightly lower persistence of the response at this time-point, most likely due to the longer interval and therefore further decay of the antibody since vaccination with rMenB+OMV NZ.

> **Comment:** This was the pivotal study submitted in adolescents. It was large and well conducted. Overall rMenB+OMV NZ found to be highly immunogenic in the adolescent subjects for all vaccination schedules. The vaccination schedules of two doses administered with an interval of one or two months showed a similarly high immune response. The response was lower in the one dose vaccine schedule; a three dose vaccine schedule provided no added immune response.

7.1.2. Other efficacy studies

7.1.2.1. Study V72P4, in adults

7.1.2.1.1. Study design, objectives, locations and dates

V72P4 was a phase 2, open-label, multi-centre study conducted in Italy and Germany between 2007-2009, in healthy at-risk adult laboratory workers routinely exposed to *N meningitidis*, The study was designed to explore the immunogenicity and safety of three doses of Novartis rMenB+OMV NZ given at 0, 2 and 6 months, and to explore the immunogenicity of a single injection of Novartis MenACWY conjugate vaccine given at 7 months, one month after the third rMenB+OMV NZ vaccination. 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.

7.1.2.1.2. Inclusion and exclusion criteria

Individuals eligible to be enrolled into this study were those:

- male and female adults 18 through 50 years of age at enrolment;
- able to comprehend and follow all required study procedures;
- who had given written consent after the nature of the study had been explained;
- who were available for all the visits scheduled in the study (i.e., not planning to leave the area before the end of the study period);
- in good health as determined by the outcome of medical history, physical examination and clinical judgment of the investigator;
- who were or might be routinely exposed to *N. meningitidis* cultures.

Exclusion criteria

Individuals not eligible to be enrolled into this study were those who:

- had household contact with and/or intimate exposure to an individual with any laboratory confirmed *N. meningitidis* infection within 60 days of enrolment;
- had experienced significant acute or chronic infection within the previous 7 days or had experienced fever (defined as axillary temperature ≥ 38°C) within the previous day;
- had received antibiotics within 6 days prior to enrolment;
- were pregnant or nursing (breastfeeding) mothers or females of childbearing age who had not used or do not plan to use acceptable birth control measures, for the 12-month duration of the study;
- suffered from any serious chronic or progressive disease (e.g., any history of neoplasm, insulin dependent diabetes, cardiovascular disease, hepatic disease, renal disease, autoimmune disease, HIV infection or AIDS, or blood dyscrasias, signs of cardiac or renal failure or severe malnutrition). Subjects who suffer from metabolic syndrome with more than 2 criteria fulfilled and/or not sufficiently controlled diseases as part of the metabolic syndrome had to be excluded (exception: subjects with mild asthma were eligible for enrolment. Subjects with moderate or severe asthma requiring chronic use of inhaled or systemic corticosteroids were not eligible for enrolment);
- had any other serious chronic disease including progressive neurological disease or seizure disorder;
- had a known or suspected impairment/alteration of the immune system, resulting from:
  - receipt of immunosuppressive therapy, including use of corticosteroids or chronic use of inhaled high-potency corticosteroids within the previous 60 days. [Use of topical corticosteroids administered during the study in limited areas of the body was allowed];
  - receipt of immunostimulants;
- had an inherited genetic anomaly (known cytogenic disorders, e.g., Down's Syndrome);
- had received blood, blood products and/or plasma derivatives, or a parenteral immunoglobulin preparation within the previous 90 days;
- had a known bleeding diathesis, or any condition that may be associated with a prolonged bleeding time;
- had a history of severe allergic reactions after previous vaccinations such as anaphylactic shock, asthma, urticaria, or other allergic reaction or hypersensitivity to any vaccine component;
- had either received, or for whom there was intent to immunize with any other vaccine(s) within 30 days prior and throughout the study period (exception: licensed flu-vaccine should not be administered within 14 days prior to enrolment);
- were obese at screening (e.g., with a body mass index [BMI] ≥ 30 where BMI reflects obesity and not high muscle mass);
- had received another investigational agent within 90 days or before completion of the safety follow-up period in another study, whichever was longer, prior to enrolment and unwilling to refuse participation in another investigational trial through the end of the study;
- had a current problem or a history of substance abuse which, in the opinion of the investigator or medical monitor, might interfere with participation in the study;

- had any condition which in the opinion of the investigator may interfere with the evaluation of the study objectives.

7.1.2.1.3. Study treatments

All subjects were enrolled to receive 3 doses of the final formulation of rMenB+OMV NZ following a 0, 2, 6-month schedule. One single dose of the Novartis Men ACWY conjugate vaccine at study month 7.

7.1.2.1.4. Efficacy variables and outcomes

The immunogenicity objectives were exploratory, and endpoints included:

- Percentage (95% CI) of subjects with hSBA ≥ 1:4 at each time point, by meningococcal B strain.
- hSBA GMTs and GMRs at each time point, by meningococcal B strain.
- Percentage (95% CI) of subjects with hSBA ≥ 1:4 at each time point, by meningococcal B strain, stratified by baseline titer ((hSBA<1:4) or (hSBA ≥1:4).

7.1.2.1.5. Randomisation and blinding methods

Subjects who met the study admission criteria were enrolled in to the study and were assigned a 5-digit subject number. The first two digits identified the study site. The next three digits identified the subject within the site and were assigned sequentially, with 001 corresponding to the first subject enrolled. The trial was designed as an open-label study; both the study personnel and the subject knew which vaccine was being administered.

7.1.2.1.6. Analysis populations

See section 7.1.1.1.6 for definitions.

7.1.2.1.7. Sample size

There were no prespecified statistical criteria.

7.1.2.1.8. Statistical methods

Subjects who were appropriately enrolled and who contributed evaluable pre- and post-vaccination serum samples were included in the per protocol immunogenicity analyses at those time points. The percentage of subjects with a BCA titer ≥ 1:4 measured at baseline, one month following the first, second vaccination, prior to and one month after the third vaccination, and two months after the third vaccination were calculated. For each strain for which BCA was measured, the percentage of subjects with a titer ≥1:4 and the associated 95% CIs was tabulated. The same analyses were performed for the percentage of subjects with a BCA titer ≥ 1:8. Additionally, the percentage of subjects with no detectable bactericidal titres at baseline (BCA <1:4) who had a detectable titer (i.e., BCA ≥1:4 or BCA ≥1:8) during the study and the associated 95% CIs were computed by time point and meningococcal strain. The percentage of subjects with at least a fourfold rise in titer over the pre-vaccination titer and the associated 95% CIs were also assessed at each time point, by meningococcal B strain. Raw unadjusted GMTs and 95% CIs , geometric mean ratios (GMRs), and associated 95% CIs were computed for each visit and meningococcal B strain by exponentiating (base 10) the means of the log-transformed (base 10) titres and their 95% CIs from PROC UNIVARIATE. Additionally, the percentage of subjects with a bactericidal complement assay (BCA) titer ≥ 1:4 against *N. meningitidis* serogroups A, C, W and Y measured at one month after the MenACWY vaccination were to be calculated. For each of the four serogroups for which BCA is measured, the percentage of subjects with a titer ≥1:4 and the associated 95% CIs were tabulated. The same analyses were performed for the percentage of subjects with a BCA titer ≥1:8. Median, minimal, and maximal titres were calculated.

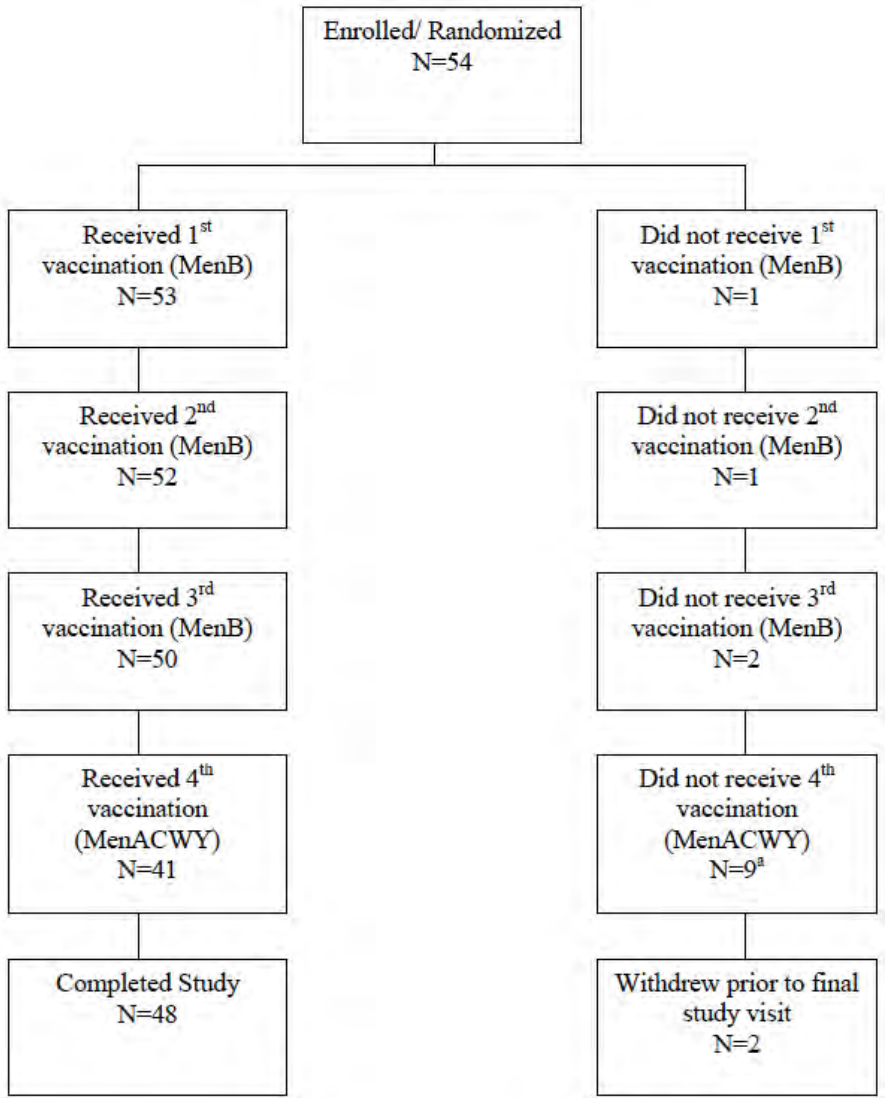
7.1.2.1.9. Participant flow

A total of 54 subjects were enrolled and 48 subjects completed the study. Six subjects withdrew due to AEs, consent withdrawal, lost to follow up and protocol deviations (Table 25 and Figure 8).

Table 25: Summary of Study Terminations V72P4 – Enrolled Population

	N (%)
Enrolled	54 (100%)
Completed study	48 (89%)
Premature withdrawals[a]	6 (11%)
Death	0
Adverse Event	2 (4%)
Withdrew consent	2 (4%)
Lost to follow-up	1 (2%)
Protocol Deviation/violation	1 (2%)

Figure 8: Subjects Completion Flowchart



[a]: These subjects did not receive study vaccination with MenACWY conjugate vaccine because the subject's previous MenACWY vaccination was considered to be too close to the scheduled time point. These subjects are considered to have completed the study protocol.

7.1.2.1.10. Major protocol violations/deviations

Major protocol deviations were reported for 32 subjects, while minor protocol deviations were reported for 6 subjects. Major deviations were mostly due to missing blood draw. Other reasons included no MenACWY vaccination and blood draw/ vaccination being out of time window (Table 26). All subjects with major protocol deviations were analysed for the safety analysis. Subjects with major protocol deviations who provided blood draw at a time point were included in the PP analysis for that time point.

Table 26: Number (%) of Subjects with Major Protocol Deviations

	N=54
Total Number of Subjects with Major Protocol Deviations:	
Major Deviation[a]	32 (59%)
Any Blood Draw Missing	30 (56%)
Any MenB Vaccination Missing	4 (7%)
Blood Draw Outside Window	7 (13%)
No MenACWY Vacc. At Visit 6	13 (24%)
No Valid Blood Results	2 (4%)
Vaccination Outside Window	11 (20%)

7.1.2.1.11. Baseline data

Overall, 54 subjects were enrolled. The immunogenicity analysis for rMenB+OMV NZ was performed on the per protocol (PP) population which included 46 subjects. The PP analysis for MenACWY included 23 subjects. The demographic and baseline characteristics were similar between enrolled and PP populations. The majority of subjects were Caucasians (96%) and 50% were female. At baseline, similar percentages (range 22% to 37%) of subjects had hSBA ≥ 1:4 across the three MenB reference strains.

7.1.2.1.12. Results for the primary efficacy outcome

Across all strains, the percentages of subjects with hSBA ≥ 1:4 increased to 80% to 88% one month after the first vaccination, 91% to 100% one month after the second vaccination, and 92% to 100% one month after the third vaccination. Between 67% (for strain NZ98/254) and 100% of subjects maintained hSBA >1:4 four months after the second vaccination, indicating good persistence of bactericidal activity after the second dose. Across the three MenB reference strains, the hSBA GMTs increased significantly (based on non-overlapping 95% CIs) over baseline one month after the first (GMR range 10 to 15), second (GMR range 17 to 63) and third (GMR range 16 to 113) vaccinations with rMenB+OMV NZ. The hSBA GMTs against all three strains fell four months after the second vaccination (GMT range 9.35 to 37), although they were still higher than the GMTs at baseline (GMR range 6.18 to 15).

7.1.2.1.13. Results for other efficacy outcomes

Subset analyses were performed for subjects with baseline hSBA < 1:4 or ≥1:4 for each of the reference strains. For subjects with baseline hSBA < 1:4, 73% to 79% had hSBA ≥ 1:4 against the three MenB strains one month after the first vaccination with rMenB+OMV NZ. One month after the second vaccination, 100% of the subjects had hSBA ≥1:4 against strains 44/76 and 5/99, and 89% against strain NZ98/254. One month after the third vaccination, 100% of the subjects had hSBA ≥1:4 against strain 5/99, while 96% and 90% of the subjects had hSBA ≥ 1:4 against strains 44/76 and NZ98/254, respectively. Also in subjects with hSBA <1:4 at baseline, there were marked increases in GMTs after the first and second doses of rMenB+OMV NZ. Further increases in GMTs were observed for strain 5/99 after the third dose. For subjects with baseline hSBA >1:4, robust increases in hSBA GMTs were also observed.

Comment: This was a small phase 2 study of rMenB+OMV NZ in healthy, at-risk adults. It appears to be well designed although there was a significant number of major deviations (mainly due to blood draw outside designated time period). The study showed that rMenB+OMV NZ can effectively induce bactericidal antibodies (irrespective of baseline titres) in adults following two doses at 0, and 2 months, as measured by hSBA against the three MenB reference strains 44/76, 5/99 and NZ98/254, and that a third dose at 6 months may not provide added benefit.

7.1.2.2. Study V72P5, in adults

7.1.2.2.1. Study design, objectives, locations and dates

V72P5 was a phase 1, observer-blind, single-centre, randomized study conducted in Switzerland in healthy adults 18 to 40 years of age. The study was the first study to explore the safety and immunogenicity of a Meningococcal B Recombinant Vaccine (rMenB) formulation with OMV purified from *N. meningitidis* serogroup B strain NZ98/254. A total of 70 adults were enrolled and randomized at a 2:2:1 ratio to receive three doses of rMenB+OMV NZ, rMenB+OMV NW, or rMenB administered on a 0, 1, and 2-month schedule. Immunogenicity was evaluated against a panel of fifteen *N. meningitidis* serogroup B strains as well as the indicator strains eventually selected for evaluation in the phase II and phase III studies.

7.1.2.2.2. Inclusion and exclusion criteria

Inclusion criteria

Individuals eligible to be enrolled into this study were those:

- male and female adults 18 through 40 years of age at enrolment;
- able to comprehend and follow all required study procedures, (i.e., able to give blood for analysis of safety and immunogenicity);
- who had given written consent after the nature of the study had been explained;
- who were available for all the visits scheduled in the study (i.e., not planning to leave the area before the end of the study period);
- in good health as determined by the outcome of medical history, physical examination, screening laboratory tests, and clinical judgment of the investigator.

Exclusion criteria

Individuals not eligible to be enrolled into this study were those who:

- had a history of any meningococcal B vaccine administration;
- had a current or previous confirmed or suspected disease caused by N meningitidis;
- had had household contact with and/or intimate exposure to an individual with any laboratory confirmed N meningitidis infection within 60 days of enrolment;
- had experienced fever (defined as axillary temperature ≥ 38.0°C) within the previous 3 days or were suffering from a current acute infection;
- had taken antibiotics within 7 days prior to enrolment (exception: other antibiotics taken once daily within 14 days after the last dose);
- were pregnant or nursing (breastfeeding) mothers or females of childbearing age who had not used or did not plan to use acceptable birth control measures for the 8-month duration of the study;
- had any serious chronic or progressive disease (e.g., any history of neoplasm, diabetes, cardiac disease, hepatic disease, autoimmune disease, HIV infection or AIDS, or blood dyscrasias, signs of cardiac or renal failure or severe malnutrition). Exception: subjects with

mild asthma were eligible for enrolment. Subjects with moderate or severe asthma requiring chronic use of inhaled or systemic corticosteroids were not eligible for enrolment;

- had any other serious chronic disease including progressive neurological disease or seizure disorder;
- had a known or suspected impairment/alteration of the immune system, resulting from receipt of immunosuppressive therapy, including use of corticosteroids or chronic use of inhaled high-potency corticosteroids within the previous 60 days or receipt of immunostimulants;
- had an inherited genetic anomaly (known cytogenic disorders, e.g., Down's Syndrome);
- had received blood, blood products, and/or plasma derivatives or a parenteral immunoglobulin preparation within the previous 90 days;
- had a known bleeding diathesis or any condition that may be associated with a prolonged bleeding time, including abnormal coagulation laboratory results at screening;
- had a history of severe allergic reactions after previous vaccinations such as anaphylactic shock, asthma, urticaria, or other allergic reaction or hypersensitivity to any vaccine component;
- had either received, or for whom there is intent to immunize with, any other vaccine(s) within 30 days prior and throughout the study period (exception: licensed flu vaccine was not to be administered within 14 days prior to enrolment);
- were obese at screening (e.g., with a body mass index [BMI] ≥ 30 where BMI reflected obesity and not high muscle mass);
- had received another investigational agent within 90 days or before completion of the safety follow-up period in another study, whichever was longer, prior to enrolment and unwilling to refuse participation in another investigational trial through the end of the study;
- had a current problem or a history of substance abuse which, in the opinion of the investigator or medical monitor, might interfere with participation in the study;
- had any condition which in the opinion of the investigator and/or the medical monitor that could interfere with the evaluation of the study objectives.

7.1.2.2.3. Study treatments

Group I: Novartis Meningococcal B Recombinant Vaccine + OMV NZ at 0, 1, and 2 months (rMenB + OMV NZ). Planned: 26 subjects.

Group II: Novartis Meningococcal B Recombinant Vaccine + OMV NW at 0, 1, and 2 months (rMenB + OMV NW). Planned: 26 subjects.

Group III: Novartis Meningococcal B Recombinant Vaccine without OMV at 0, 1, and 2 months (rMenB). Planned: 13 subjects.

7.1.2.2.4. Efficacy variables and outcomes

The immunogenicity objectives were purely exploratory.

Primary immunogenicity endpoints included percentage of subjects with hSBA ≥ 1:4, GMTs against a panel of genetically distinct meningococcal strains prior to the first dose, one month after the third dose, and 6 months after the third dose. A secondary immunology analysis examined percentages of subjects with hSBA ≥ 1:4, and GMTs at one month after the second dose.

7.1.2.2.5. Randomisation and blinding methods

Subjects who met the study admission criteria were enrolled into the study and were assigned a 5-digit subject number. The first two digits identified the study site. The next three digits identified the subject within the site and were assigned sequentially; 001 corresponded to the first subject enrolled (i.e., subject 01001 corresponded to the first subject enrolled at the site 01). Subjects were randomly assigned in a 2:2:1 ratio to one of the vaccination group.

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, and were instructed not to reveal the identity of the study vaccines either to the subject or to the investigative site personnel (investigator, study nurse) involved in the monitoring or conduct of the trial, except in an emergency. Designated individuals were not to have contact with the subjects after the administration of the study vaccines. If the study vaccine code was supplied to the investigator in the event of an emergency, the study monitor was to be notified immediately by the investigator.

7.1.2.2.6. Analysis populations

See section 7.1.1.1.6 for definitions.

7.1.2.2.7. Sample size

Including 26 subjects in each of groups I and II and 13 subjects in group III provided 95% confidence intervals as for several possible observed adverse event rates and observed proportions of subjects responding to immunization (i.e., proportion of subjects with BCA ≥ 1:4) from 0% to 100%. The actual enrolment was 70 subjects, 28 subjects in groups I and II and 14 subjects in group III.

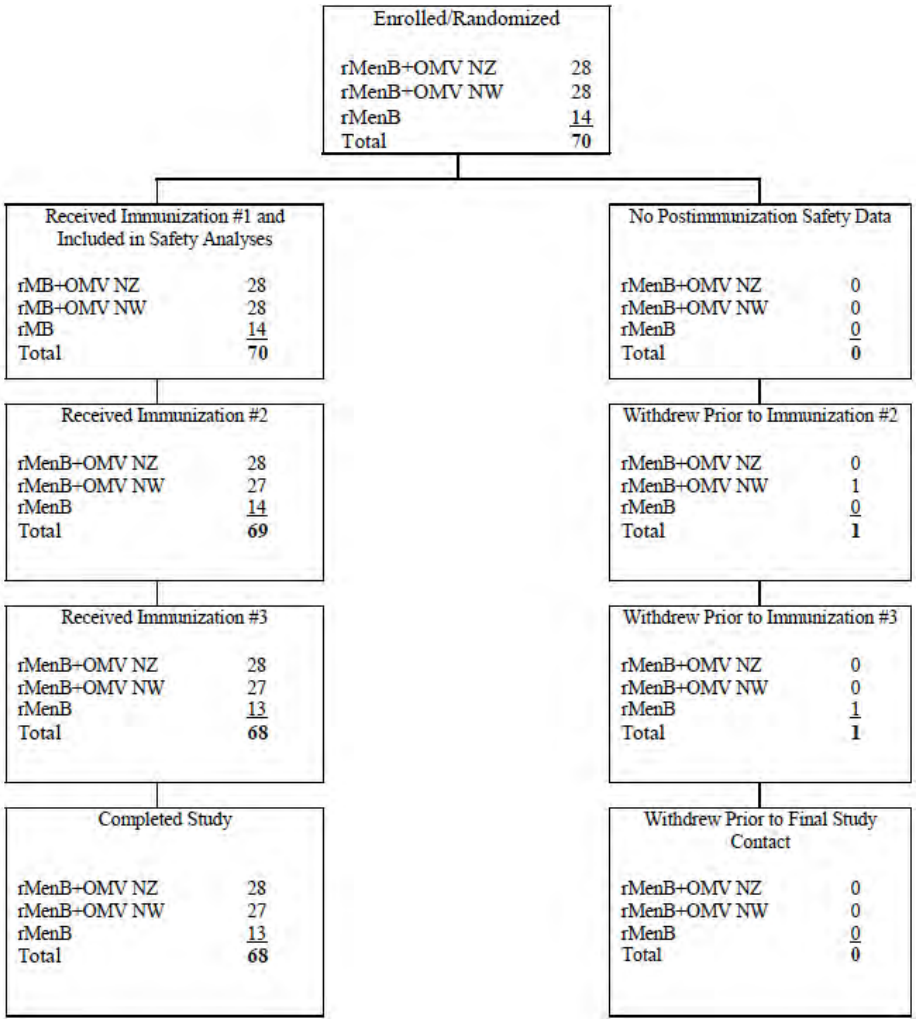
7.1.2.2.8. Statistical methods

There were no prespecified statistical criteria. The statistical tables and graphs were generated using SAS 9.1 or higher (SAS Institute, Cary, NC).

7.1.2.2.9. Participant flow

All subjects in the rMenB + OMV NZ group completed the study per protocol. One subject (4%) in the rMenB + OMV NW group and one subject (7%) in the rMenB group discontinued due to withdrawn consent. The flowchart in Figure 9 displays by vaccine group the number of subjects in the study at each visit, the number of subjects who withdrew from the study at various stages, and the number of subjects who completed the study.

Figure 9: Subject Disposition Flowchart



7.1.2.2.10. Major protocol violations/deviations

Protocol deviations were reported for 3 subjects in the study.

- Subject **[Information redacted]** in the rMenB + OMV NW group did not receive the second or third immunization and did not have blood drawn at visits 5, 7, and 8. This subject withdrew consent on study day 243.
- Subject **[Information redacted]** in the rMenB group did not receive the third immunization and did not have blood drawn at visits 5, 7, and 8. This subject withdrew consent on study day 245.
- Subject **[Information redacted]** in the rMenB + OMV NW group had the third blood draw outside the time interval required after the third immunization (drawn on day 39 instead of on day 26-37).

7.1.2.2.11. Baseline data

The immunogenicity per protocol (PP) population included all subjects who received all the relevant doses of vaccine correctly, provided evaluable serum samples at the relevant time points, and had no major protocol violation as defined prior to analysis. All 28 subjects in the rMenB + OMV NZ group, 27 of 28 subjects (96%) in the rMenB + OMV NW group, and 13 of 14 subjects (93%) in the rMenB group were included in the PP population. The all-enrolled population was identical to the safety population. 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 (64% in the rMenB + OMV NZ group, 57% in the rMenB + OMV NW group, and 86% in the rMenB group). Most subjects from all vaccine groups were Caucasian (89% both in the rMenB + OMV NZ group and in the rMenB + OMV NW group and 86% in the rMenB group). Mean subject weight on enrolment 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.

7.1.2.2.12. Results for the primary efficacy outcome

In the rMenB+OMV NZ group (N=28), 96% had hSBA ≥ 1:4 against strain NZ98/254 at 1 month after the second dose, and the percentage remained high at 93% after the third dose. Against strains 5/99 and 44/76, 100% of subjects achieved hSBA ≥ 1:4 after the second dose and after the third dose (Table 27). The results show that 2 vaccinations with rMenB+OMV NZ induced a good immunological response in adults, with 96% to 100% of subjects reaching the protective hSBA >4 postvaccination.

7.1.2.2.13. Results for other efficacy outcomes

In the rMenB + OMV NZ group and the rMenB + OMV NW group, the proportion of subjects with bactericidal titres ≥ 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, Table 27. For 4 of the strains (44/76, 5/99, CU385, and MC58), all subjects in all vaccine groups achieved bactericidal titres ≥ 1:4 at 1 month after the third vaccination. Ninety-three percent of the subjects in the rMenB + OMV NZ group achieved bactericidal titres ≥ 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 titres ≥ 1:4 at 1 month after the third dose. At 1 month after the third vaccination, all subjects in all vaccine groups had bactericidal titres ≥ 1:4 against 4 or more of the 15 tested strains. Furthermore, all subjects (100%) in the rMenB + OMV NZ group, 25/27 (93%) subjects in the rMenB + OMV NW group, and 12/13 (92%) subjects in the rMenB group had bactericidal titres ≥ 1:4 against 7 or more of the strains.

Table 27: Proportion of Subjects with Bactericidal Titres ≥ 1:4 (95% CI) at One Month After the Third Vaccination, by Meningococcal B Strain

Strain	Time point	rMenB + OMV NZ N=28	rMenB + OMV NW N=27	rMenB N=13
1000	Pre-vaccination	50% (31-69%)	37% (19-58%)	54% (25-81%)
	1 month after 3rd vacc.	86% (67-96%)	78% (58-91%)	54% (25-81%)
2996	Pre-vaccination	32% (16-52%)	33% (17-54%)	23% (5-54%)
	1 month after 3rd vacc.	86% (67-96%)	74% (54-89%)	62% (32-86%)
H44/76	Pre-vaccination	32% (16-52%)	30% (14-50%)	54% (25-81%)
	1 month after 3rd vacc.	100% (88-100%)	100% (87-100%)	100% (75-100%)
5/99	Pre-vaccination	43% (24-63%)	59% (39-78%)	31% (9-61%)
	1 month after 3rd vacc.	100% (88-100%)	100% (87-100%)	100% (75-100%)
95N477	Pre-vaccination	7% (1-24%)	15% (4-34%)	0% (0-25%)
	1 month after 3rd vacc.	7% (1-24%)	15% (4-34%)	0% (0-25%)
CU385	Pre-vaccination	32% (16-52%)	56% (35-75%)	54% (25-81%)
	1 month after 3rd vacc.	100% (88-100%)	100% (87-100%)	100% (75-100%)
GB013	Pre-vaccination	21% (8-41%)	30% (14-50%)	38% (14-68%)
	1 month after 3rd vacc.	79% (59-92%)	63% (42-81%)	77% (46-95%)
GB364	Pre-vaccination	32% (16-52%)	56% (35-75%)	46% (19-75%)
	1 month after 3rd vacc.	100% (88-100%)	92% (75-99%)[a]	92% (64-100%)
M1390	Pre-vaccination	50% (31-69%)	59% (39-78%)	77% (46-95%)
	1 month after 3rd vacc.	96% (82-100%)	96% (81-100%)	92% (64-100%)
M3812	Pre-vaccination	25% (11-45%)	26% (11-46%)	46% (19-75%)
	1 month after 3rd vacc.	79% (59-92%)	70% (50-86%)	85% (55-98%)
M4105	Pre-vaccination	29% (13-49%)	30% (14-50%)	31% (9-61%)
	1 month after 3rd vacc.	100% (88-100%)	70% (50-86%)	46% (19-75%)
M4458	Pre-vaccination	21% (8-41%)	27% (12-48%)[b]	23% (5-54%)
	1 month after 3rd vacc.	70% (50-86%)[c]	73% (52-88%)[d]	77% (46-95%)
M6190	Pre-vaccination	11% (2-28%)	26% (11-46%)	38% (14-68%)
	1 month after 3rd vacc.	43% (24-63%)	37% (19-58%)	46% (19-75%)
MC58	Pre-vaccination	54% (34-72%)	52% (32-71%)	69% (39-91%)
	1 month after 3rd vacc.	100% (88-100%)	100% (87-100%)	100% (75-100%)
NZ98/254	Pre-vaccination	18% (6-37%)	22% (9-42%)	31% (9-61%)
	1 month after 3rd vacc.	93% (76-99%)	74% (54-89%)	54% (25-81%)

Ninety-three percent of the subjects in the rMenB + OMV NZ group achieved bactericidal titres ≥1:4 against strain NZ98/254 at 1 month after the third dose, while this percentage was lower in the rMenB + OMV NW group (74%) and in the MenB group (54%). For all other strains, similar percentages of subjects (ranging from 37% to 100%) in the three vaccine groups achieved bactericidal titres ≥ 1:4 at 1 month after the third dose, and at this time point all subjects in all vaccine groups had bactericidal titres ≥ 1:4 against 4 or more of the 15 tested strains. Furthermore, all subjects (100%) in the rMenB + OMV NZ group, 93% of the subjects in the rMenB + OMV NW group, and 92% of the subjects in the rMenB group had bactericidal titres ≥ 1:4 against 7 or more of the 15 strains. Although the proportion of subjects with bactericidal titres ≥ 1:4 at 1 month after the third dose was the primary immunogenicity variable, these high proportions of subjects with bactericidal titres ≥ 1:4 were also observed at 1 month after the second vaccination. After the second vaccination, all subjects in all vaccine groups had bactericidal titres ≥ 1:4 against 4 or more of the 15 tested strains, and all subjects (100%) in the rMenB + OMV NZ group, 96% in the rMenB + OMV NW group, and 92% in the rMenB group had bactericidal titres ≥ 1:4 against 7 or more of the 15 strains. Similar trends were observed when analysing only subjects with no detectable baseline bactericidal titres, when analysing bactericidal titres ≥ 1:8, or when analysing GMTs and GMRs of bactericidal titres. No major differences were observed between the proportion of subjects with at least 4-fold rise in

bactericidal titres at 1 month after the second vaccination and at 1 month after the third vaccination, i.e., the subjects achieving a 4-fold rise did so after two vaccinations.

At 1 month after the third vaccination, geometric mean anti-287-953, anti-936-741, anti-961c, anti-OMV NW, and anti-OMV NW ELISA IgG concentrations were raised compared to baseline in all three vaccine groups. Similar ELISA GMRs were observed for 287-953, 936-741, and 961c in the different vaccine groups, while GMRs for OMV NW and OMV NZ were higher for the OMV-based vaccines (rMenB OMV NZ and rMenB OMV NW) than for the vaccine without OMV (rMenB). Although decreases in bactericidal titres and ELISA concentrations were more common than increases there was no consistent trend in the immunogenicity results when comparing the results from 6 months after the third vaccination with the results from 1 month after the third vaccination.

Long-term B cell memory responses were measured as B lymphocytes directed against the protein-protein fusions 287-953 and 936-741 and the individual protein antigen 961c at 6 months after the third vaccination. Increases in B lymphocytes compared to baseline were observed in all three vaccine groups.

> **Comment:** This was an early, phase 1 study in adults that compared three formulations of MenB vaccination. The rMenB OMV NZ was found to be more immunogenic than the rMenB OMV NW and both were more immunogenic than the vaccine without OMV. From the results of this trial, it was decided to move forward with the rMenB OMV NZ in subsequent clinical studies.

7.1.2.3. Study V72P6, in infants

7.1.2.3.1. Study design, objectives, locations and dates

V72P6 was a phase 2, open label, multi-centre, controlled, randomized study conducted in the UK between 2006-2008 in healthy infants aged 2 months at time of enrolment. The study explored the safety and immunogenicity of rMenB or rMenB+OMV NZ when administered to healthy infants at 2, 4 and 6 months of age, followed by a fourth dose at 12 months of age. All subjects were also to receive the recommended UK routine infant vaccinations. A total of 147 children were enrolled (150 were planned) and randomized at a 2:2:1:1 ratio to receive either rMenB or rMenB+OMV NZ (administered at 2, 4, 6, and 12 months of age) or a single dose of rMenB or rMenB+OMV NZ at 12 months of age. Six months after the third dose (primary infant series), the subjects received a fourth dose and were followed up for a further 6-month period.

7.1.2.3.2. Inclusion and exclusion criteria

Inclusion criteria

Subjects eligible to be enrolled in the study:

- healthy 2-month old infants (55-89 days, inclusive), 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 provided written informed consent after the nature of the study had been explained;
- those available for all the visits scheduled in the study;
- those in good health as determined by the clinical judgment of the investigator.

Exclusion criteria

Individuals were not to be enrolled into the study:

- whose parents/legal guardians were unwilling or unable to give written informed consent to participate in the study;
- who had previously received any meningococcal B vaccine;

- who had received prior vaccination with DTP (acellular or whole cell), IPV or OPV, *H influenzae* type b (Hib) or PC7 vaccine;
- who had a previous ascertained or suspected disease caused by *N meningitidis*, *S pneumoniae*, *C diphtheriae*, *tetani*, Poliovirus, Hib, or *B pertussis* (history of laboratory confirmed, or clinical condition of spasmodic cough for a period ≥2 weeks associated with apnoea or whooping);
- who had household contact with and/or intimate exposure to an individual with laboratory confirmed *N meningitidis, B pertussis*, Hib, *C diphtheriae* or Polio infection since birth;
- who had a history of any anaphylactic shock, asthma, urticaria or other allergic reaction after previous vaccinations or known hypersensitivity to any vaccine component;
- who had experienced significant acute or chronic infection within the previous 7 days or had experienced fever (≥38.0°C) within the previous 3 days;
- who had any present or suspected serious acute or chronic disease (e.g., with signs of cardiac, renal failure, hepatic disease, or severe malnutrition or insulin dependent diabetes), or progressive neurological disease, or a genetic anomaly/known cytogenic disorders (e.g., Down's syndrome);
- who had leukaemia, lymphomas;
- who had a known or suspected autoimmune disease or impairment/alteration of immune function;
- with a suspected or known HIV infection or HIV related disease;
- who had ever received blood, blood products and/or plasma derivatives or any parenteral immunoglobulin preparation from birth and for the full length of the study;
- with a known bleeding diathesis, or any condition that might be associated with a prolonged bleeding time;
- who had experienced any seizure, either associated with fever or as part of an underlying neurological disorder or syndrome;
- who had taken antibiotics within 7 days prior to enrolment (exception: antibiotics taken once daily within 14 days after the last dose);
- who had either received, or for whom there was intent to immunize with any other vaccine(s), with respect to the study vaccines, within 30 days prior and throughout the study period;
- who had ever received another investigational agent from birth prior to enrolment and unwilling to refuse participation in another investigational trial through the end of the study;
- whose parents/legal guardians, were planning to leave the area of the study site before the end of the study period;
- with any condition which, in the opinion of the investigator, might interfere with the evaluation of the study objectives.

7.1.2.3.3. Study treatments

Subjects were randomly assigned in a 2:2:1:1 ratio to one of the following vaccination group(s) to receive:

- Group I: Routine Immunizations + Novartis rMenB Vaccine without OMV-NZ at 2, 4, 6 and 12 months

- Group II: Routine Immunizations + Novartis rMenB Vaccine with OMV-NZ at 2, 4, 6 and 12 months
- Group III: Routine Immunizations + Novartis rMenB Vaccine without OMV-NZ at 12 months
- Group IV: Routine Immunizations + Novartis rMenB Vaccine with OMV-NZ at 12 months

Dosage regimen of Novartis rMenB Vaccine with or without OMV-NZ:

1 4 doses of 0.5 mL each (Groups I and II)

2. 1 dose of 0.5 mL each (Groups III and IV)

as shown in Table 28

Table 28: Study Treatments in V72P6

Group	Vaccine	Vaccination Age
rMenB	Routine vaccinations + Novartis rMenB vaccine	2, 4, 6, and 12 months (rMenB)
rMenB + OMV	Routine vaccinations + Novartis rMenB vaccine + OMV NZ	2, 4, 6, and 12 months (rMenB + OMV)
Routine	Routine vaccinations + Novartis rMenB vaccine	12 months (rMenB)
Routine+OMV	Routine vaccinations + Novartis rMenB vaccine + OMV NZ	12 months (rMenB + OMV)

Route of administration of Novartis rMenB Vaccine with or without OMV-NZ: IM into the anterolateral area of the right thigh. The study vaccines were supplied as a full liquid formulation in a pre-filled syringe containing 0.5 mL.

Dosage regimen of routine immunizations (all study Groups):

1. Pediacel: 3 doses of 0.5 mL each
2. Prevnar: 3 doses of 0.5 mL each
3. Menjugate: 2 doses of 0.5 mL each
4. MMR: 1 dose of 0.5 mL each
5. Menitorix: 1 dose of 0.5 mL each

7.1.2.3.4. Efficacy variables and outcomes

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 (BCA) response against a panel of genetically distinct meningococcal strains.

Secondary

- To explore the immunogenicity of Novartis rMenB Vaccine +/- OMV-NZ at 30 days after the second dose by evaluation of the breadth of BCA response against a Novartis Vaccines and panel of genetically distinct meningococcal strains.
- To explore the antibody persistence of Novartis rMenB Vaccine +/- OMV-NZ at 12 months of age, by evaluation of the breadth of BCA response against a panel of genetically distinct meningococcal strains.

- To explore the immunogenicity of Novartis rMenB Vaccine +/- OMV-NZ at 30 days after the fourth dose (administered at 12 months of age), by evaluation of the breadth of BCA response against a panel of genetically distinct meningococcal strains.
- To explore the immunogenicity of Novartis rMenB Vaccine +/- OMV-NZ at 30 days after the administration of a single dose given at 12 months of age, by evaluation of the breadth of BCA 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 second, the third and the fourth dose of Novartis rMenB Vaccine +/- OMV-NZ (Groups I and II) and at 30 days after the single dose administration (Groups III and IV).

7.1.2.3.5. Randomisation and blinding methods

Subjects who met the study admission criteria were enrolled into the study and assigned a 5-digit subject number. The first two digits identify the study site and the remaining three digits were assigned sequentially, with 001 corresponding to the first subject enrolled. Subjects were randomly assigned in a 2:2:1:1 ratio to one of the vaccination groups, following a randomization list created by the Biostatistics and Statistical Reporting department, Novartis.

7.1.2.3.6. Analysis populations

See section 7.1.1.1.6 for definitions.

7.1.2.3.7. Sample size

A total of 147 subjects were enrolled and immunized so as to obtain 120 evaluable subjects, allowing for a 20% drop out rate.

7.1.2.3.8. Statistical methods

Due to small sample sizes, the immunogenicity analyses were purely exploratory. No statistical tests were performed. Primary immunogenicity endpoints included percentage of subjects with hSBA ≥ 1:4, and GMTs against a panel of genetically distinct meningococcal strains prior to the first dose, and one month after the third dose. A secondary immunology analysis examined percentages of subjects with hSBA ≥ 1:4 and GMTs at one month after the second dose, and at 12 months of age and one month later. All the above-mentioned criteria were also analysed stratified by pre-vaccination titer (i.e. baseline hSBA < 1:4 and ≥1:4). There were no prespecified statistical criteria.

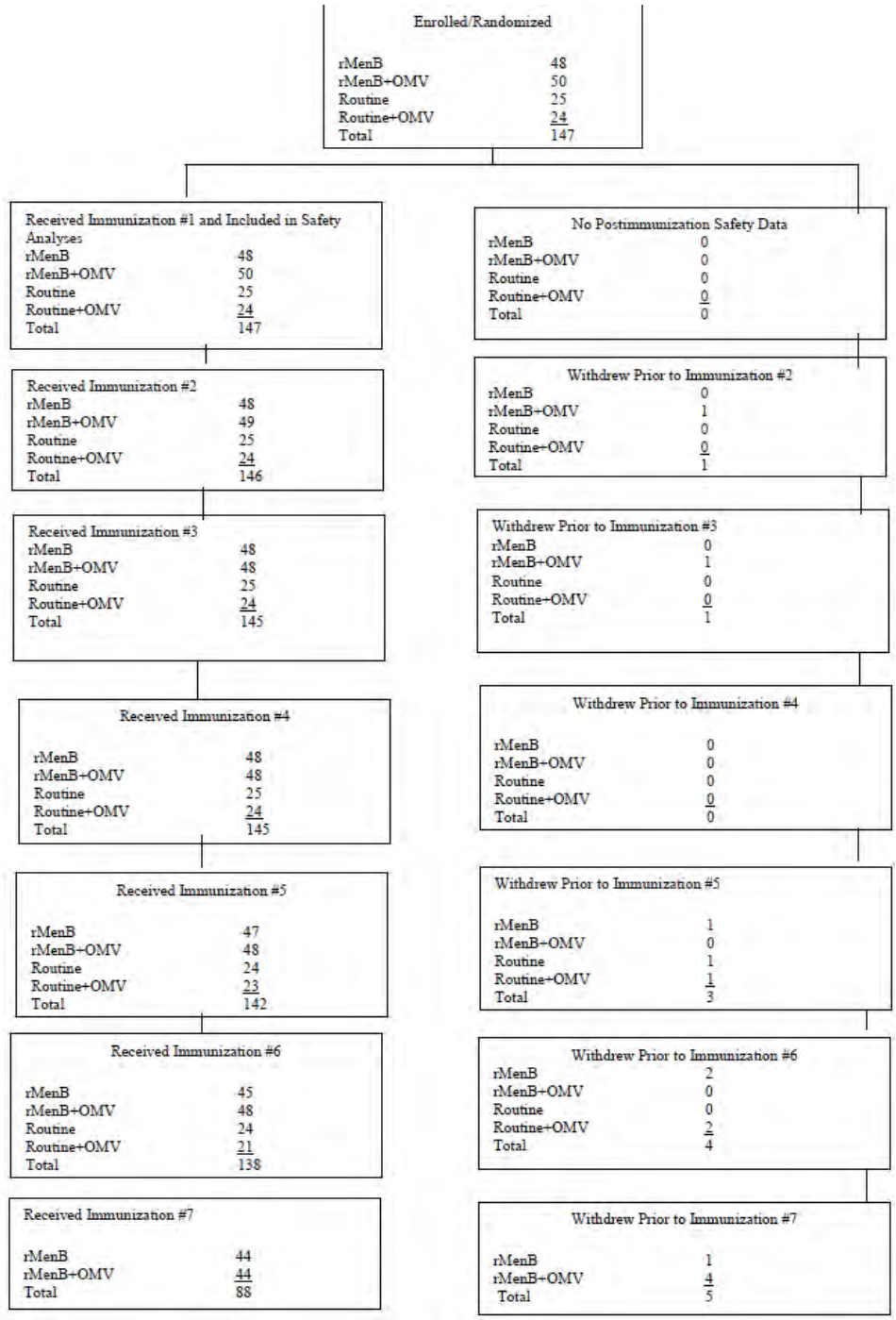
7.1.2.3.9. Participant flow

Of the 147 infants enrolled subjects, 135 (92%) completed the study. There were twelve premature withdrawals: four in the rMenB group, five in the rMenB+OMV group, one in the Routine group, and two in the Routine+OMV group. In the rMenB group, of the four withdrawals, three subjects were lost to follow-up and one withdrew consent. In the rMenB+OMV group, of the five withdrawals, three subjects withdrew consent and two were lost to follow-up. In the Routine group, the only premature withdrawal was due to a protocol deviation. In the Routine+OMV group, of the two withdrawals, one subject withdrew consent and the other was lost to follow-up (Table 29). The flow through the study is shown in Figure 10.

Table 29: Summary of Study Terminations – Randomized Population

	Number (%) of Subjects				
Vaccine Group	rMenB[a]	rMenB+OMV[a]	Routine[b]	Routine+OMV[b]	All
Enrolled	48	50	25	24	147
Completed study	44 (92%)	45 (90%)	24 (96%)	22 (92%)	135 (92%)
Premature withdrawals	4 (8%)	5 (10%)	1 (4%)	2 (8%)	12 (8%)
Withdrawal of consent	1 (2%)	3 (6%)	0	1 (4%)	5 (3%)
Lost to follow-up	3 (6%)	2 (4%)	0	1 (4%)	6 (4%)
Protocol deviation/violation	0	0	1 (4%)	0	1 (<1%)

Figure 10: Subject disposition flowchart



7.1.2.3.10. Major protocol violations/deviations

Protocol deviations, both major and minor, were similar across the vaccine groups (98 *vs.* 97). All subjects enrolled in the study satisfied the eligibility criteria at the time of enrolment. Ninety-eight major protocol deviations were observed in 58 subjects. A higher number of major protocol deviations were observed in the rMenB+OMV group as compared to the rMenB group (49 *vs.* 31) while they were similar between the Routine±OMV groups (both 9). All subjects with major protocol deviations were analysed for the safety analysis and were excluded from the PP immunogenicity analysis, while all subjects with minor protocol deviations were not excluded from any analysis set. There were 98 major deviations from the protocol in 58 subjects. Subjects who missed blood draws (48) or who were vaccinated outside extended window (37). One subject received the wrong vaccine or didn't receive the rMenB vaccine (13).

7.1.2.3.11. Baseline data

Overall, 147 infants were enrolled and randomized (2:2:1:1) in this study, 48 in the rMenB group, 50 in the rMenB+OMV group, 25 in the Routine group and 24 in the Routine+OMV group (Table 30). Of this total, 79 (41 in the rMenB group and 38 in the rMenB+OMV group) subjects were included in the Per Protocol (PP) population at one month after second injection and 77 subjects (37 in the rMenB group and 40 in the rMenB+OMV group) 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 (38 in the rMenB group, 30 in the rMenB+OMV group and 22 in each of the Routine groups). The PP population included all subjects in the MITT population without a major protocol deviation.

Table 30: Population Analysed

Population	rMenB [a] N=48	rMenB+OMV [a] N=50	Routine [b] N=25	Routine+OMV [b] N=24
Enrolled	48(100%)	50(100%)	25(100%)	24(100%)
Immunized	48(100%)	50(100%)	25(100%)	24(100%)
Immunogenicity ITT	46(96%)	46(92%)	24(96%)	23(96%)
PP Post 2nd	41(85%)	38(76%)	0	0
PP Post 3rd	37(77%)	40(80%)	0	0
PP Post-Booster Or 1st Vacc.	38(79%)	30(60%)	22(88%)	22(92%)
Safety	48(100%)	50(100%)	25(100%)	24(100%)

Demographics and other baseline characteristics of all subjects were similarly distributed among study groups except that more male subjects were enrolled in the groups receiving a single dose of rMenB (males,64%) or rMenB+OMV NZ (males,71%) at 12 months of age. 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.

7.1.2.3.12. Results for the primary efficacy outcome

One month after the second vaccination, at 5 months of age, 95% of subjects in the rMenB+OMV NZ group (N=45) achieved hSBA ≥1:4 against strain 44/76, and all subjects (100%) achieved hSBA ≥1:4 against strain 5/99. For the NZ98/254 strain, 74% achieved hSBA ≥1:4. GMTs post second dose were 28, 104 and 6.55 One month after the third vaccination with rMenB+OMV NZ, at 7 months of age, the proportions of subjects achieving hSBA ≥1:4 were 87%, 95% and 85% for strain 44/76, 5/99 and NZ98/254, respectively. Corresponding GMTs post third dose were 30, 126 and 19. At 12 months of age (pre-booster at 6 months after the third dose), bactericidal

activity persisted against strains 44/76 and 5/99 with the proportion of subjects with hSBA ≥4 ranging from 68% to 88%. Bactericidal antibodies did not persist as well against strain NZ98/254 with 36% of subjects immunized with rMenB+OMV NZ as infants maintaining hSBA ≥1:4 at 12 months of age. One month after the 4th or booster injection with rMenB+OMV NZ at 12 months of age, the proportion of subjects achieving hSBA ≥1:4 were 100%, 97% and 94% against strains 44/76, 5/99 and NZ98/254, respectively. Corresponding GMTs post fourth dose were 106, 629 and 29. These GMTs were markedly higher compared to the GMTs in subjects who received a single dose of rMenB+OMV NZ at 12 months of age (6.02, 8 and 1.66 for strains 44/76, 5/99 and NZ98/254).

Proportion of subjects with bactericidal titres ≥1:4 and ≥1:8

One month after the third vaccination, at 6 months of age, the proportion of subjects achieving bactericidal titres ≥1:4 against 44/76-SL strain ranged from 78% [28/36] to 87% [34/39] in the rMenB±OMV groups and for the 5/99 strain, ranged from 95% [35/37] to 100% [32/32] in the rMenB±OMV groups. For the NZ98/254 strain, one month after the third vaccination, 34 subjects (85%) in the rMenB+OMV group achieved bactericidal titres ≥1:4, while only 2 subjects (5%) developed bactericidal activity at this titer in the rMenB group. As stated previously, a minimal BCA response against strain NZ98/254 was expected for the rMenB group (without OMV) since this strain is measuring BCA primarily directed against PorA P1.4 in the OMV vaccine component.

At 12 months of age (prebooster at 6 months after the third dose), BCA persisted well against strains 44/76-SL and 5/99 in the in the rMenB±OMV groups with the proportion of subjects with titres ≥1:4 ranging from 68% to 92%. Bactericidal antibodies did not persist as well against strain NZ98/254 with 36% of subjects immunized with rMenB+OMV as infants maintaining bactericidal titres ≥1:4 at 12 months of age. In comparison, acting as controls, the proportion of subjects with titres ≥1:4 at baseline (pre-vaccination) at 12 months of age in the Routine±OMV groups was markedly lower against all three MenB strains, ranging from 0% to 18%. One month after the 4th or booster injection at 12 months of age, the proportion of subjects achieving bactericidal titres ≥1:4 against strain 44/76-SL and strain 5/99 were 100% and 97%, respectively, in the rMenB±OMV groups. For the NZ98/254 strain, one month after the 4th or booster injection, one subject (3%) in the rMenB group and 29 subjects (94%) in the rMenB+OMV group achieved bactericidal titres ≥1:4.

The Routine±OMV groups received a single dose of rMenB±OMV vaccine at 12 months of age and served as comparators for the booster response in the rMenB±OMV groups. The proportion of subjects achieving bactericidal titres ≥1:4 against the three MenB strains was consistently lower for the Routine±OMV groups receiving a single dose at 12 months of age as compared to the fourth dose response in the rMenB±OMV groups at the same age. The only exception was for the Routine group against strain 5/99, in which 100% of subjects receiving a single dose of rMenB vaccine achieved bactericidal titres ≥1:4 (21/21 subjects), compared to the rMenB±OMV groups in which 97% of subjects vaccinated with a 4th dose of rMenB or rMenB+OMV vaccine achieved bactericidal titres ≥1:4 against strain 5/99. The higher proportion of subjects with bactericidal titres observed in the rMenB±OMV groups, who were vaccinated with three doses in infancy, indicates the induction of immunological memory in these infants following the infant vaccination series at 2, 4 and 6 months of age. The trends observed in subjects with bactericidal titres ≥1:8 across all three strains were similar to the trends observed in subjects with bactericidal titres ≥1:4.

7.1.2.3.13. Results for other efficacy outcomes

Proportion of subjects with four-fold rise in bactericidal titer

One month after the third vaccination, the percentage of subjects achieving a four-fold increase above baseline ranged from 69% (25/36) to 85% (33/39) against strain 44/76- SL and from 92% (34/37) to 97% (31/32) against strain 5/99 in the rMenB±OMV groups. For the NZ98/254

strain, a four-fold rise above baseline was achieved by one subject in the rMenB group and by 31 (78%) subjects in the rMenB+OMV group. When bactericidal antibody persistence was measured at 6 months after the 3rd vaccination (prebooster) as four-fold rises compared to the original baseline, bactericidal antibodies persisted well against strains 5/99 and 44/76-SL in both vaccine groups (from 41% to 84% of subjects) and least against strain NZ98/254 (2% the rMenB and 23% the rMenB+OMV).

Bactericidal immune responses after the 4th or booster injection at 12 months of age in the rMenB±OMV groups, when analysed by the percentage of subjects achieving a four-fold increase above the original baseline, showed similar results to the previous analysis based on the percentage of subjects achieving bactericidal titres ≥1:4. The proportion of subjects achieving four-fold rises in bactericidal titres against both strain 44/76-SL and strain 5/99 was 97% in the rMenB±OMV groups. For the NZ98/254 strain, one month after the 4th or booster vaccination, one subject (3%) in the rMenB group and 26 subjects (84%) in the rMenB+OMV group achieved four-fold rises in bactericidal titer. Similar trends were observed when four-fold rises were determined from the prebooster baseline at 12 months of age. In contrast, the proportion of subjects achieving four-fold rises against the three MenB strains was consistently lower for the Routine±OMV groups receiving a single dose at 12 months of age as compared to the 4th dose response in the rMenB±OMV groups. At one month post vaccination, the percentage of subjects achieving a four-fold increase above baseline ranged from 14% to 36% against strain 44/76-SL and from 59% to 100% against strain 5/99 for the Routine±OMV groups. For the NZ98/254 strain, a four-fold rise above baseline was achieved by no subject in the Routine group and by 2 (9%) subjects in the Routine+OMV group.

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

At one month after the third vaccination, robust rises in GMTs and GMRs were observed against the 5/99 strain and 44/76-SL in both the rMenB and rMenB+OMV vaccine groups. In general, lower GMTs and GMRs were observed against the NZ98/254 strain. As expected, GMTs and GMRs showed minimal response against strain NZ98/254 for the rMenB group without OMV. Bactericidal antibody GMTs at 12 months of age persisted well against strains 5/99 and 44/76-SL in both vaccine groups (GMTs from 4.49 to 38) and least well against strain NZ98/254 (GMTs from 1.16 to 2.42). Bactericidal immune responses after the 4th or booster injection at 12 months of age in the rMenB±OMV groups, when summarized by GMTs and GMRs, showed very robust booster responses across all three MenB strains, except for no detectable response against strain NZ98/254 by rMenB vaccinees as expected. In comparison, rises in GMTs and GMRs against the three MenB strains were markedly lower for the Routine±OMV groups receiving a single dose at 12 months of age as compared to the 4th dose response in the rMenB±OMV groups.The higher bactericidal titres observed in the rMenB±OMV groups demonstrate the presence of immunological memory in these subjects following the three-dose vaccination series at 2, 4 and 6 months of age, as compared to the naïve subjects who received their first dose of vaccine at 12 months of age in the Routine±OMV groups.

> **Comment:** This was a well conducted phase 2 study. The immunogenicity results demonstrated that the rMenB+OMV NZ formulation could effectively induce bactericidal antibodies in infants following three doses at 2, 4 and 6 months of age. The responses could be further boosted with a 4th dose of rMenB+OMV NZ at 12 months of age, demonstrating that the infants had been primed with the three doses and immunological memory had been generated. This study provided sufficient evidence of immune responses to warrant the further development and evaluation of rMenB+OMV NZ vaccine in infants in phase 3.

7.1.2.4. Study V72P9, in infants

7.1.2.4.1. Study design, objectives, locations and dates

V72P9 was a phase 2, single blind, single centre randomized study conducted in the UK in 2007-8. The study explored the safety and immunogenicity of three doses of rMenB or rMenB+OMV

NZ in healthy infants 6-8 months of age at the time of enrolment. Three vaccinations with rMenB+OMV NZ were administered intramuscularly (IM) at enrolment, (6-8 months of age), two months later, and at 12 months of age. The three injections of rMenB Vaccine ± OMV were administered intramuscularly (IM) at enrolment, (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 enrolment 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

7.1.2.4.2. Inclusion and exclusion criteria

Inclusion criteria

Subjects eligible to be enrolled in the study were:

- Healthy 6-8 months old infants;
- For whom a parent/legal guardian have given written informed consent after the nature of the study has been explained;
- Available for all the visits scheduled in the study;
- In good health as determined by clinical judgment of the investigator.

Exclusion criteria

Infants not to be enrolled in the study were:

- Whose parents/legal guardians unwilling or unable to give written informed consent to participate in the study;
- Who had previously received any meningococcal B vaccine;
- Who had a previous ascertained or suspected disease caused by N. meningitidis;
- Who had household contact with and/or intimate exposure to an individual with laboratory confirmed N. meningitidis;
- Who had a history of any anaphylactic shock, asthma, urticaria or other allergic reaction after previous vaccinations or known hypersensitivity to any vaccine component;
- Who had experienced fever (defined as axillary temperature ≥38.0°C) within the previous 3 days or are suffering from a present acute infectious disease;
- Who had any present or suspected serious acute or chronic disease (e.g. with signs of cardiac, renal failure, hepatic disease, or severe malnutrition or insulin dependent diabetes), or progressive neurological disease, or a genetic anomaly/known cytogenic disorders (e.g., Down's syndrome);
- Who had leukaemia, lymphomas;
- Who had a known or suspected autoimmune disease or impairment/alteration of immune function resulting from (for example):
  - receipt of any immunosuppressive therapy
  - receipt of any systemic corticosteroid or ACTH or inhaled steroids in dosages which are associated with hypothalamic-pituitary-adrenal axis suppression (e.g., 1 mg/kg/day of prednisone [or its equivalent])

- chronic use of inhaled high-potency corticosteroids (e.g., budesonide 800 µg per day or fluticasone 750 µg per day);

· With a suspected or known HIV infection or HIV related disease;

· Who had ever received blood, blood products and/or plasma derivatives or any parenteral immunoglobulin preparation in the past 12 weeks and for the full length of the study;

· With a known bleeding diathesis, or any condition that may be associated with a prolonged bleeding time;

· Who had experienced any seizure, either associated with fever or as part of an underlying neurological disorder or syndrome;

· Who had received antibiotics within 6 days prior to enrolment;

· Who had either received, or for whom there is intent to immunize with any other vaccine(s), with respect to the study vaccines, within 30 days prior and throughout the study period. [Exception: the applicable routine immunization (e.g. MMR, MCC-Hib, PC7) are allowed];

· Had received another investigational agent within 90 days or before completion of the safety follow-up period in another study, whichever is longer, prior to enrolment and unwilling to refuse participation in another investigational trial through the end of the study;

· Whose parents/legal guardians, were planning to leave the area of the study site before the end of the study period;

· With any condition which, in the opinion of the investigator, might interfere with the evaluation of the study objectives.

The investigator was able to withdraw a subject if, in his or her clinical judgment, it was in the best interest of the subject or if the subject could not comply with the protocol. In addition, a subject may have been withdrawn from the study due to the occurrence of the following events:

· Febrile convulsions and neurological disturbances after vaccination

· Hypersensitivity to the investigational vaccine

· Other suspected side effects that could compromise the subject's wellbeing.

Where the withdrawal of a subject resulted from an adverse event, this was to be documented and, the tests and evaluations listed for the termination visit were to be carried out, if possible.

7.1.2.4.3. Study treatments

A total of 60 children were enrolled (60 were planned) and randomized at a 1:1 ratio to receive either rMenB or rMenB+OMV NZ, with two doses administered at 6 to 8 or 8 to 10 months of age, and the third dose at 12 months of age. Subjects were followed up for 6 months after the last dose. The study vaccines were supplied as a full liquid formulation in a pre-filled syringe containing 0.5 mL. The investigator was responsible for the administration of the vaccine to subjects enrolled into the study according to the procedures stipulated in this study protocol.

7.1.2.4.4. Efficacy variables and outcomes

The main efficacy variables were:

· To explore the immunogenicity of rMenB Vaccine ± OMV when administered to healthy infants, at 30 days after the second and the third injection, by evaluation of the breadth of bactericidal activity (BCA) response against a panel of genetically distinct meningococcal strains.

- To explore the safety and tolerability of Novartis rMenB with or without OMV throughout the clinical study.

7.1.2.4.5. Randomisation and blinding methods

Subjects who met the study admission criteria were enrolled into the study and were assigned a 5-digit subject number. The first two digits identify the study site (always '01' in this case). The next three digits identify the subject within the site and were assigned sequentially, with 001 corresponding to the first subject enrolled. Subjects were randomly assigned in a 1:1 ratio to one of the vaccine groups, following a randomization list created by the Biostatistics and Statistical Reporting department, Novartis. The trial was designed as a single-blind study with the study personnel being aware of the vaccine administered, but the enrolled subjects and their parents unaware of the vaccine received.

7.1.2.4.6. Analysis populations

See section 7.1.1.1.6 for definitions.

7.1.2.4.7. Sample size

Sixty (60) subjects were to be enrolled and to receive one of two investigational vaccines in this Phase 2 study, 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 BCA in healthy infants 6-8 months old.

7.1.2.4.8. Statistical methods

The data were analysed by Novartis Vaccines and Diagnostics, as defined in the Analysis Plan (AP). Any data analyses carried out independently by the investigator were to be submitted to Novartis Vaccines and Diagnostics, before publication or presentation. The statistical tables and graphs were generated using SAS 9.1 (SAS Institute, Cary, NC).

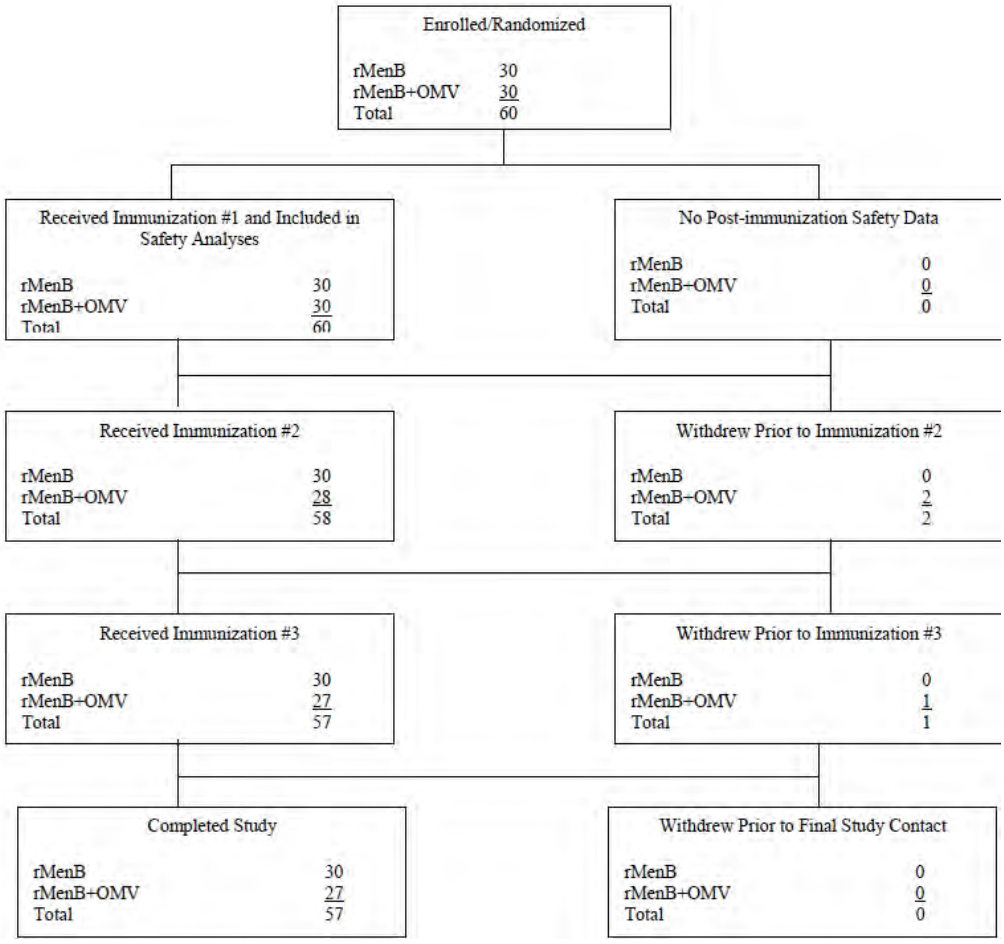
7.1.2.4.9. Participant flow

Of the 60 enrolled subjects, 57 completed the study (Table 31); three subjects who did not complete the study were from the rMenB+OMV group, two of whom withdrew consent and one was lost to follow up. The participant flow is shown in Figure 11.

Table 31: Summary of Study Termination in V72P9

	Number (%) of Subjects		
Vaccine Group	**rMenB (N=30)**	**rMenB + OMV (N=30)**	**Total**
Enrolled	30 (100%)	30 (100%)	60 (100%)
Discontinued	0	3 (10%)	3 (5%)
Completed study	30 (100 %)	27 (90 %)	57 (90%)
Reason for Discontinuation			
Protocol violation	0	0	0
Adverse event	0	0	0
Withdrawal of consent	0	2 (7%)	2 (7%)
Lost to follow-up	0	1 (3 %)	1 (3 %)

Figure 11: Subject Disposition flowchart in V72P9



7.1.2.4.10. Major protocol violations/deviations

Protocol deviations, both major and minor, were balanced among the rMenB and rMenB+OMV group. Major protocol deviations were reported for 13 subjects (6 in the rMenB group and 7 in the rMenB+OMV group), while minor protocol deviations were reported for 36 subjects (13 in rMenB group and 23 in rMenB+OMV group). All subjects with major protocol deviations were analysed for the safety analysis and were excluded from the PP immunogenicity analysis, while all subjects with minor protocol deviations did not result in subject exclusion from any analysis set. There were 19 major deviations from the protocol in 13 subjects. These were all a failure to have a blood draw.

7.1.2.4.11. Baseline data

Demographic and other baseline characteristics were similar between the rMenB and rMenB+OMV NZ groups. The majority of subjects was Caucasian and balanced between the vaccine groups. Overall 57 subjects received all three injections, including 27 in the rMenB+OMV NZ group. Of these, 24 were evaluated for immunogenicity (Table 32).

Table 32: Overview of Subject Population

Population	Vaccination Groups	
	rMenB (N=30)	rMenB + OMV (N=30)
Enrolled	30 (100%)	30 (100%)
Immunized	30 (100%)	30 (100%)
Safety Population	30 (100%)	30 (100%)
Modified Intent to Treat	25 (83%)	24 (80%)
Per Protocol	25 (83%)	24 (80%)
Per Protocol-Visit 3	25 (83%)	23(77%)
Per Protocol-Visit 5	24 (80%)	24 (80%)

7.1.2.4.12. Results for the primary efficacy outcome

One month after the second vaccination, hSBAs ≥ 1:4 were achieved by 100% of these subjects against strains 44/76SL and 5/99, and by 95% against NZ98/254. These percentages were essentially unchanged one month after the third vaccination (100%, 100% and 96%). There were marked increases in GMTs and GMRs after the second and third vaccinations with rMenB+OMV NZ as compared to baseline against all 3 reference strains. Higher GMTs were attained following the third dose compared to the second dose for strains 5/99 and NZ98/254; GMTs were similar following the second and third doses against strain 44/76. For the 287-953 protein antigen, all subjects (100%) achieved fourfold rises in IgG antibody concentrations, with increases in geometric mean concentrations (GMC) and geometric mean ratios (GMR) in both the vaccination groups after the second as well as the third injections, as measured by ELISA.

Comment: This phase 2 study was well designed and efficacy results demonstrated that the rMenB+OMV NZ formulation could effectively induce bactericidal antibodies in older infants following two doses at approximately 6 and 8 months of age, as measured by hSBA against strains 44/76, 5/99 and NZ98/254. The third dose administered in this study at 12 months of age resulted in higher GMTs compared to the second dose for strains 5/99 and NZ98/25.

7.1.2.5. Study V72P12, in infants

7.1.2.5.1. Study design, objectives, locations and dates

V72P12 was a phase 2b, open label, multi-centre, parallel-group, randomized study conducted in the UK, Spain, Italy, Belgium, Germany and Czech Republic in healthy infants approximately 2 months of age at time of enrolment between 2008-2010. The study assessed the safety and immunogenicity of rMenB+OMV NZ when administered with or without routine infant vaccinations (Infanrix Hexa and Prevenar) to healthy infants in their first year of life according to different vaccination schedules (2, 4, 6 or 2, 3, 4 months of age). This study was also aimed to demonstrate that the immunogenicity of routine infant vaccines when given concomitantly with rMenB+OMV NZ at 2, 3 and 4 months of age was non-inferior to that of routine infant vaccines given without rMenB+OMV NZ.

7.1.2.5.2. Inclusion and exclusion criteria

Inclusion criteria

Subjects eligible for enrolment in the study were:

- 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 (or both parents, if required by local laws) had given written informed consent after the nature of the study had been explained;
- available for all the visits scheduled in the study;

- in good health as determined by medical history, physical examination and clinical judgment of the investigator.

Exclusion criteria

- History of any meningococcal B or C vaccine administration;
- Prior vaccination with any Diphtheria, Tetanus, Pertussis (acellular or whole cell), Polio (either Inactivated or Oral), *Haemophilus influenzae* type b (Hib), and pneumococcal antigens;
- Previous ascertained or suspected disease caused by *N. meningitidis*;
- Household contact with and/or intimate exposure to an individual with laboratory confirmed *N. meningitidis*;
- History of severe allergic reaction after previous vaccinations or hypersensitivity to any vaccine component;
- Significant acute or chronic infection within the previous 7 days or axillary temperature ≥38°C within the previous day;
- Antibiotics within 6 days prior to enrolment;
- Any serious chronic or progressive disease according to the judgment of the investigator (e.g., neoplasm, insulin dependent diabetes mellitus Type I, cardiac disease, hepatic disease, progressive neurological disease or seizure, either associated with fever or as part of an underlying neurological disorder or syndrome, autoimmune disease, HIV infection or AIDS, or blood dyscrasias or diathesis, signs of cardiac or renal failure or severe malnutrition);
- Known or suspected impairment/alteration of the immune system, immunosuppressive therapy, use of systemic corticosteroids or chronic use of inhaled high-potency corticosteroids since birth;
- Receipt of blood, blood products and/or plasma derivatives or any parenteral immunoglobulin preparation;
- Receipt of, or intent to immunize with any other vaccine (s) (with the exception of rotavirus), within 30 days prior and throughout the study period;
- Participation in another clinical trial since birth or planned for during study;
- Family members and household members of research staff;
- Any condition which, in the opinion of the investigator, might interfere with the evaluation of the study objectives.

7.1.2.5.3. Study treatments

A total of 1885 children were enrolled (1800 were planned) and randomized at a 2:2:1:1 ratio to receive three injections of rMenB+OMV NZ administered at either 2, 4, and 6 or 2, 3, and 4 months of age with concomitant vaccines or at 2, 4, and 6 months of age without concomitant vaccines or to receive routine infant vaccines alone administered at 2, 3, and 4 months of age. Subjects were followed up for 6 months after the last (primary series) vaccination.

7.1.2.5.4. Efficacy variables and outcomes

The primary immunogenicity 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 and 2, 3 and 4 months of age, as measured by percentage of subjects with human serum bactericidal activity (hSBA) titer ≥1:5, at one month after the third vaccination (i.e., for Groups 1 and 3). For the rMenB+OMV NZ Groups 1-3 and the Routine group 4, percentages of subjects with hSBA titres ≥1:5 at one month after the third vaccination and associated 95% CIs were

computed for each strain. The immune response for the Norwegian strain 44/76, New Zealand strain NZ98/254 and strain 5/99 would be deemed sufficient for Group 1 (B+R246= rMenB+OMV + concomitant vaccines at 2, 4, 6) and Group 3 (B+R234 = rMenB + OMV+concomitant vaccines at 2, 3, 4) if the lower limit of the two-sided 95% CI for the % ≥1:5 was ≥70%.

The first secondary objective was 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 (i.e., comparing Groups 3 and 4). The immune response 30 days after last vaccination with B. pertussis, diphtheria and tetanus toxoid, H. influenzae type b, polio 1, 2, 3, hepatitis B and the seven antigens of the heptavalent pneumococcal conjugate vaccine was measured by ELISA or Neutralization assay for subjects in Group 3 (B+R234) and Group 4 (R234 = concomitant vaccines only, at 2,3 and 4 months of age). The percentage of subjects with antibody response against the antigens of the routine vaccinations above a pre-specified cut-off level, at baseline and 30 days after the last injection were determined; the associated 95 CIs were computed for each routine antigen for both vaccine groups.

7.1.2.5.5. Randomisation and blinding methods

Subjects who met the study admission criteria were enrolled into the study and were assigned a 6-digit subject number. The first two digits identified the study site while the third digit the possible satellite. The next three digits identified the subject within the site and were assigned sequentially, with 001 corresponding to the first subject enrolled. The trial was designed as an open-label study; both the study personnel and the subject's parent (s)/legal guardian (s) knew which vaccine was being administered. The laboratory testing was performed blinded to group allocation.

7.1.2.5.6. Analysis populations

See section 7.1.1.1.6 for definitions.

7.1.2.5.7. Sample size

The primary objective was to demonstrate the sufficiency of rMenB+OMV NZ immune response in groups 1 and 3, as measured by percentage of subjects with hSBA titer ≥1:5 when administered to healthy infants at 2, 4 and 6 (group 1) and 2, 3 and 4 (group 3) months of age, at 1 month after the third vaccination.

Based on the antibody response of infants in the V72P6 Novartis study who received 3 doses of the rMenB+OMV NZ (N=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% (44/76), 86% (NZ98/254) and 95% (5/99) respectively (non-interpolated hSBA results). The primary criterion for a sufficient immune response was that the 2-sided 95% LCL for the percentage of subjects with a hSBA titer ≥ 1:5 at 1 month following the third vaccination was ≥70% for strains 44/76, NZ98/254 and 5/99. Assuming that the infants of this study receiving vaccine either according to the 2, 4, 6 or the 2, 3, 4 schedule would have similar antibody responses as the infants from the V72P6 study, distributions of the 2-sided 95% LCL for the proportion with hSBA titer ≥1:5 were constructed by performing 5000 simulations for underlying true proportions ranging from 80% to 95%, and for various group sizes (N =240, 300).

7.1.2.5.8. Statistical methods

The statistical evaluation of the results was performed by BCDM as predefined in the AP. The statistical tables and graphs were generated using SAS version 9.1.

7.1.2.5.9. Participant flow

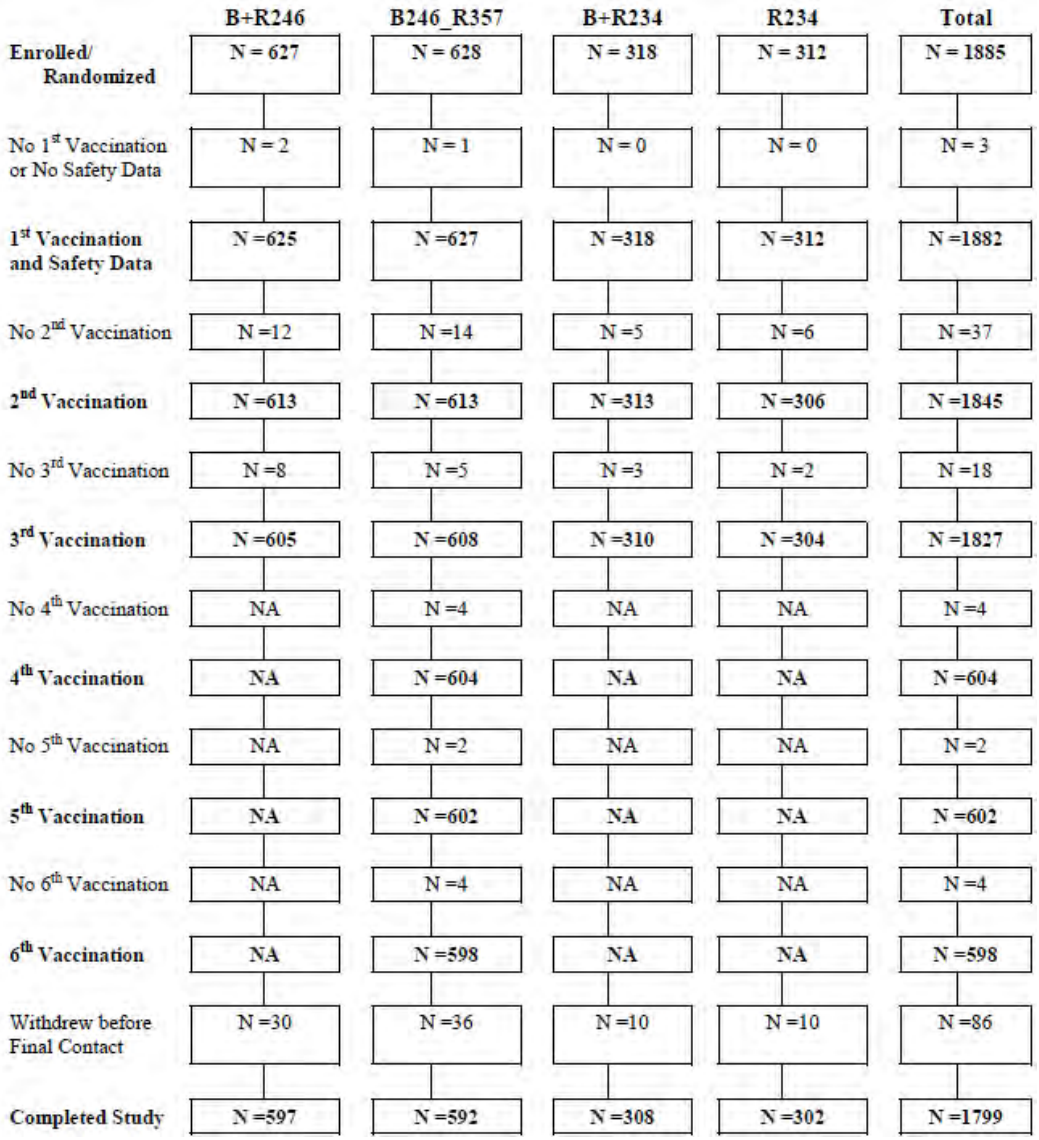
A total of 1885 subjects were enrolled and 1799 subjects completed the study. In all, 86 subjects withdrew due to AEs, consent withdrawal, lost to follow up, inappropriate enrolment,

administrative reasons and protocol deviations (Table 33). No deaths were reported in this study. Participant flow is shown in Figure 12.

Table 33: Summary of Study Terminations – Enrolled Population

Group	Group 1	Group 2	Group 3	Group 4	Total
Schedule	**B+R246**	**B246_R357**	**B+R234**	**R234**	
Enrolled	627	628	318	312	1885
Completed study	597 (95%)	592 (94%)	308 (97%)	302 (97%)	1799 (95%)
Premature withdrawals	30 (5%)	36 (6%)	10 (3%)	10 (3%)	86 (5%)
AEs	4 (<1%)	7 (1%)	2 (<1%)	0	13 (<1%)
Withdrew consent	12 (2%)	15 (2%)	3 (<1%)	7 (2%)	37 (2%)
Lost to follow-up	7 (1%)	9 (1%)	3 (<1%)	3 (<1%)	22 (1%)
Inappropriate enrollment	0	2 (<1%)	0	0	2 (<1%)
Administrative reason	3 (<1%)	0	1 (<1%)	0	4 (<1%)
Protocol deviations	4 (<1%)	3 (<1%)	1 (<1%)	0	8 (<1%)

Figure 12: Subject Disposition Flowchart in V72P12



7.1.2.5.10. Major protocol violations/deviations

Major protocol deviations were reported for 288 subjects, while minor protocol deviations were reported for 891 subjects. Major deviations were mostly due to missing blood draws, subjects not completing the vaccination course, or blood draw outside window visit.

7.1.2.5.11. Baseline data

The demographic and other baseline characteristics were balanced across the different vaccination groups with the majority of the subjects (93%) being Caucasian. A total of 1667 (88%) and 1630 subjects (86%) of the enrolled 1885 subjects were included in the immunogenicity MITT and PP analyses, respectively.

7.1.2.5.12. Results for the primary efficacy outcome

The primary criterion for a sufficient immune response to rMenB+OMV NZ at 30 days after the third vaccination was that the lower limit of the 2-sided 95% confidence interval (LCL) for the percentage of subjects with hSBA ≥ 1:5 should be equal to or greater than 70% for the reference strains 44/76, NZ98/254 and 5/99. The immune response at one month after the third dose met the pre-specified criteria for the groups receiving rMenB+OMV NZ with concomitant routine vaccinations against all three of the meningococcal reference strains in both the MITT and PP populations: in the MITT population, the 2-sided 95% LCLs for percentages of subjects with hSBA ≥1:5 in the two rMenB+OMV NZ plus concomitant routine vaccinations groups were 98% and 97% (strain 44/76), 98% and 99% (strain 5/99) and 75% and 76% (strain NZ98/254). The primary objective was achieved.

7.1.2.5.13. Results for other efficacy outcomes

The antibody responses to the routine vaccine antigens including diphtheria, tetanus, pertussis, poliovirus types 1,2,3, hepatitis B, PRP-Hib, and 6 of the 7 pneumococcal antigens (except PnC 6B) when given concomitantly with rMenB+OMV NZ at 2, 3 and 4 months of age were non-inferior to those to the routine vaccinations when given alone (for PnC 6B, the 2-sided 95% LCL was -14%). The non-inferiority of antibody responses to the pertussis antigens were also evaluated utilizing GMCs; the statistical criterion for success called for a LCL on the 95% CI for the ratio of GMCs 1 month after the third vaccination of ≥0.67. The non-inferiority of antibody responses against rMenB+OMV NZ when given concomitantly with routine vaccinations at 2,4 and 6 months of age to responses against rMenB+OMV NZ when given alone (i.e., with routine vaccinations given at 3, 5 and 7 months of age) was demonstrated for strain 44/76 and for strain 5/99 (2-sided 95% LCLs: -1% for both strains), but not for strain NZ98/254 (2-sided 95% LCL: -12%). Higher GMTs as measured by hSBA were seen in the subjects who received the rMenB+OMV NZ vaccination separately from the routine vaccinations.

> **Comment:** This was a large, well conducted international, phase 2B study that examined the immunogenicity of rMenB+OMV NZ, in schedules either one or two months apart, commencing at 2 months, either concomitantly or separated from other childhood vaccinations. Overall, there was a robust and sufficient bactericidal antibody response observed after 3 doses of rMenB+OMV NZ in this large population of infants in all groups. The immunogenicity results support the use of rMenB+OMV NZ, either with or without concomitant routine infant vaccines, at either the 2, 4 and 6-month schedule or the accelerated 2, 3 and 4-month schedule.

7.1.2.6. Study V72P13E1, in infants

7.1.2.6.1. Study design, objectives, locations and dates

This extension study, V72P13E1, enrolled subjects (now toddlers) who completed the parent study V72P13. Subjects who received three doses of rMenB+OMV NZ as infants in study V72P13 (both observer-blinded, safety only subjects and open label, immunogenicity subjects) were randomized in a 1:1 ratio to receive either a fourth (booster) dose of rMenB+OMV NZ at 12

months of age co-administered with routine combined measles, mumps, rubella and varicella vaccine (MMRV) or a booster dose of rMenB+OMV NZ alone at 12 months of age, followed by MMRV vaccination at 13 months of age. The control subjects from study V72P13 who received routine immunizations only (open-label, immunogenicity subjects in V72P13), were randomized at a 3:1 ratio to receive either i) MMRV alone at 12 months of age followed by two doses of rMenB+OMV NZ at 13 and 15 months of age or ii) two doses of rMenB+OMV NZ, one at 12 months of age (with concomitant MMRV) and one at 14 months of age. The other control subjects from Study V72P13 who received routine immunizations co-administered with Menjugate (observer-blinded, safety only subjects in V72P13), were randomized at a 1:1 ratio to receive either: i) a single dose of rMenB+OMV NZ together with MMRV at 12 months of age or: ii) a single dose of rMenB+OMV NZ at 12 months of age, followed by MMRV vaccination at 13 months of age.

7.1.2.6.2. Inclusion and exclusion criteria

Inclusion criteria

- 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;
- available for all the visits scheduled in the study;
- in good health as determined by medical history, physical examination and clinical judgment of the investigator.

Exclusion criteria

- Previous ascertained or suspected disease caused by N. meningitidis;
- Household contact with and/or intimate exposure to an individual with laboratory confirmed *N. meningitidis*;
- History of severe allergic reaction after previous vaccinations or hypersensitivity to any vaccine component;
- Significant acute or chronic infection within the previous 7 days or axillary temperature ≥38°C within the previous day;
- Antibiotics within 6 days prior to enrolment;
- Any serious chronic or progressive disease according to the judgment of the investigator (e.g., neoplasm, diabetes mellitus Type I, cardiac disease, hepatic disease, progressive neurological disease or seizure, either associated with fever or as part of an underlying neurological disorder or syndrome, autoimmune disease, HIV infection or AIDS, or blood dyscrasias or diathesis, signs of cardiac or renal failure or severe malnutrition);
- Known or suspected impairment/alteration of the immune system, immunosuppressive therapy, use of systemic corticosteroids or chronic use of inhaled high-potency corticosteroids since birth;
- Receipt of blood, blood products and/or plasma derivatives or any parenteral immunoglobulin preparation;
- Receipt of, or intent to immunize with another vaccine, within 30 days prior to enrolment.
- Participation in a clinical trial other than Study V72P13 since birth or planned for during this extension study;
- Family members and household members of research staff;

- Any condition which, in the opinion of the investigator, might interfere with the evaluation of the study objectives.

7.1.2.6.3. Study treatments

These are summarised in Table 34.

Table 34: Study Design and Group Descriptions in V72P13E1

In V72P13		Group in V72P13E1	Vaccinations in V72P13E1
Open label subset:	rMenB+OMV NZ + routine vaccinations at 2, 4 and 6 months of age.	12B12M (1a)	At 12 months: **rMenB+OMV NZ, MMRV**
		12B13M(1b):	At 12 months: **rMenB+OMV NZ** At 13 months: **MMRV**
	Routine vaccinations at 2, 4 and 6 months of age	12M13B15B(2a)	At 12 months: **MMRV** At 13 months: **rMenB+OMV NZ** At 15 months: **rMenB+OMV NZ**
		12M12B14B(2b)	At 12 months: **rMenB+OMV NZ, MMRV** At 14 months: **rMenB+OMV NZ**
Observer-blind subset:	rMenB+OMV NZ + routine vaccinations at 2, 4 and 6 months of age	12B12M (3a)	At 12 months: **rMenB+OMV NZ, MMRV**
	rMenB+OMV NZ + routine vaccinations at 2, 4 and 6 months of age	12B13M(3b)	At 12 months: **rMenB+OMV NZ** At 13 months: **MMRV**
	Menjugate + routine vaccinations at 2, 4 and 6 months of age	12B12M_C (4a)	At 12 months: **rMenB+OMV NZ, MMRV**
	Menjugate + routine vaccinations at 2, 4 and 6 months of age	12B13M_C(4b)	At 12 months: **rMenB+OMV NZ** At 13 months: **MMRV**

Subjects were immunised with rMenB+OMV NZ as described above as well as the following commercial vaccines, which were not part of any of the study evaluations:

- One dose of Meningococcal C vaccine (all subjects in Italy, Germany, Austria and Finland, who were enrolled in the observer-blind part)
- One booster dose of Prevenar (all subjects)
- One booster dose of InfanrixHexa, as stated in the parent trial protocol (all subjects, except for subjects enrolled in those countries where the vaccination with DTPa-HBV-IPV/Hib vaccine was provided by the public health system under the rule of law, e.g. Czech Republic)
- The second dose of PriorixTetra (all subjects)

The above mentioned non-investigational vaccines were given during the course of the trial, according to the local vaccination schedule and/or according to the applicable SPC. They were to be administered at least 30 days after the last study vaccination.

7.1.2.6.4. Efficacy variables and outcomes

The primary criterion to determine a sufficient immune response was that for the percentage of subjects with hSBA ≥ 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 analysed descriptively by hSBA GMTs, ratios of GMTs, percentage of subjects with hSBA titres ≥ 1:5 and difference in percentages of subjects with hSBA titres ≥ 1:5.
- The persistence of antibodies was evaluated descriptively by hSBA GMTs and percentage of subjects with hSBA titer ≥ 1:5 in 12-month-old toddlers.
- The immune response after a two-dose series in naive toddlers was evaluated descriptively by hSBA GMTs and percentage of subjects with hSBA titres ≥ 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 (GMTPost-dose 4 / GMTPost-dose 1) was ≥ 2.0.

7.1.2.6.5. Randomisation and blinding methods

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, until the database for V72P13 was unblinded. Half of the subjects who were enrolled in the observer-blind part of the parent trial had already received 3 doses of Menjugate vaccine and have therefore received a 4th dose. Safety data from previous studies with Menjugate vaccine evaluating 4 doses of Menjugate vaccine were available. Therefore, it was not necessary to unblind the treatment information of the V72P13 observer-blind part. 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 (Group 12B12M (1a): N = 180, Group 12B13M (1b): N = 180, Group 12M13B15B: N = approximately 380 and Group 12M12B14B: N = approximately 125). 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). Subjects who received rMenB+OMV NZ + routine vaccination in the parent trial were randomized into Group 12B12M (3a) or 12B13M (3b) in a 1:1 ratio in the extension trial. Subjects who received MenC and routine vaccination in V72P13 were randomized into Group 12B12M_C or 12B13M_C in a 1:1 ratio.

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.

7.1.2.6.6. Analysis populations

See section 7.1.1.1.6 for definitions.

7.1.2.6.7. Sample size

Based on the antibody response of infants in the Novartis V72P6 study who received 4 doses of the rMenB+OMV NZ (N=43 or 44) vaccine at 2, 4, 6 and 12 months of age, the percentage of subjects with a SBA titer ≥1:4 (non-interpolated data) at one month after the fourth vaccination was 100%, 93% and 98% for the reference strains 44/76, NZ98/254 and 5/99, respectively. Using this for calculations, at least 120 participants were necessary. With N = 150 evaluable subjects for Groups 12B12M (1a) and 12M13B15B, the overall power was 86.1%, obtained as the multiplication of each separate power for each test. To account for a drop-out of approximately 17%, 180 subjects were planned to be enrolled in Group 12B12M (1a) and 383 subjects were planned to be enrolled in Group 12M13B15B, of which the first 180 were to be randomly selected for MMRV analysis. Therefore, with 150 evaluable subjects in group 12B12M (1a) and 90 evaluable subjects.

in group 12M12B14B, the overall power to differentiate a fourth dose response from a naïve response would be 85% assuming the true increase associated with a fourth dose was at least a 5-fold increase in GMT, assuming that the strain responses were independent.

7.1.2.6.8. Statistical methods

The main analysis of the study was to be performed on the following data: 1) the complete set of immunogenicity data generated for both rMenB+OMV NZ and MMRV vaccines and 2) all safety data collected for 30 days after each subject's last administration of rMenB+OMV NZ. A clinical study report was to be written based on the main analysis. Longer term safety data collected for six months after each subject's last administration of rMenB+OMV NZ was to be provided in an addendum to the clinical study report. The main population was the Per Protocol population (PP). Immunogenicity analyses were possibly to be performed on both PP and modified ITT (MITT) population.

Primary immunogenicity:

The primary objective was to demonstrate a sufficient immune response, as measured by the percentage of subjects with SBA ≥1:5 at one month after the fourth (booster) dose of rMenB+OMV NZ, given either with or without MMRV at 12 months of age to toddlers previously primed with three doses of rMenB+OMV NZ as infants. Percentages of subjects with SBA titres ≥1:5 and associated 95% CI were computed for each strain for group 12B12M (1a) and 12B13M (1b). Raw percentages and their CIs were calculated. 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% for each of the three serogroup B reference strains.

Secondary immunogenicity:

Demonstration of non-inferiority of MMRV immune responses when administered concomitantly with the fourth (booster) dose of rMenB+OMV NZ at 12 months of age compared to MMRV given alone. The percentages of subjects with antibody response against the antigens of MMRV above a pre-specified level (Table 35) and associated 95% CIs were calculated for groups 12B12M (1a) and 12M13B15B (2a). Additionally, Group 12B12M (1a) minus group 12M13B15B (2a) differences in these percentages and associated 95% CIs were computed by a categorical linear model with factor of vaccine group. Immunogenicity of MMRV concomitantly with the fourth (booster) dose of rMenB+OMV NZ (group 12B12M (1a)) at 12 months of age was considered noninferior to MMRV given alone (group 12M13B15B (2a)) if for each 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%.

The specified cut-off level for seroconversion for each of MMRV and seroprotection for Varicella were defined in the table below:

Table 35: Specified cut-off level for immunity to antigens in other vaccines

Antigens	Cut-off for baseline inclusion in the analysis	Definition of post-vaccination response
Measles Seroconversion	<255mIU/mL	≥255mIU/mL
Mumps Seroconversion	<10 ELISA Ab units	≥10 ELISA Ab units
Rubella Seroconversion	<10 IU/mL	≥10 IU/mL
Varicella Seroconversion	<1.25 gp ELISA units/ml	≥1.25 gp ELISA units/ml
Varicella Seroprotection	<5 gp ELISA units/ml	≥5 gp ELISA units/ml

Assessment of immune response, as measured by SBA GMTs and percentage of subjects with SBA titres ≥1:5 at one month after the fourth (booster) dose of rMenB+OMV NZ, given either with or without MMRV at 12 months of age to toddlers previously primed with three doses of rMenB+OMV NZ as infants. Adjusted GMTs, geometric mean ratios (GMRs) and associated 95% CI were computed for each strain. The GMTs and 95% CIs were constructed by exponentiating (base 10) the least square means of the logarithmically transformed (base 10) titres and their 95% CIs obtained from a two-way Analysis of Variance (ANOVA) with factors for vaccine group and country.

Percentages of subjects with SBA titres ≥1:5 and associated 95% CIs were computed for each strain. Raw percentages and their CIs were calculated. Evaluation of antibody persistence as measured by SBA GMTs and percentage of subjects with SBA titres ≥1:5 in 12-month-old previously primed toddlers.

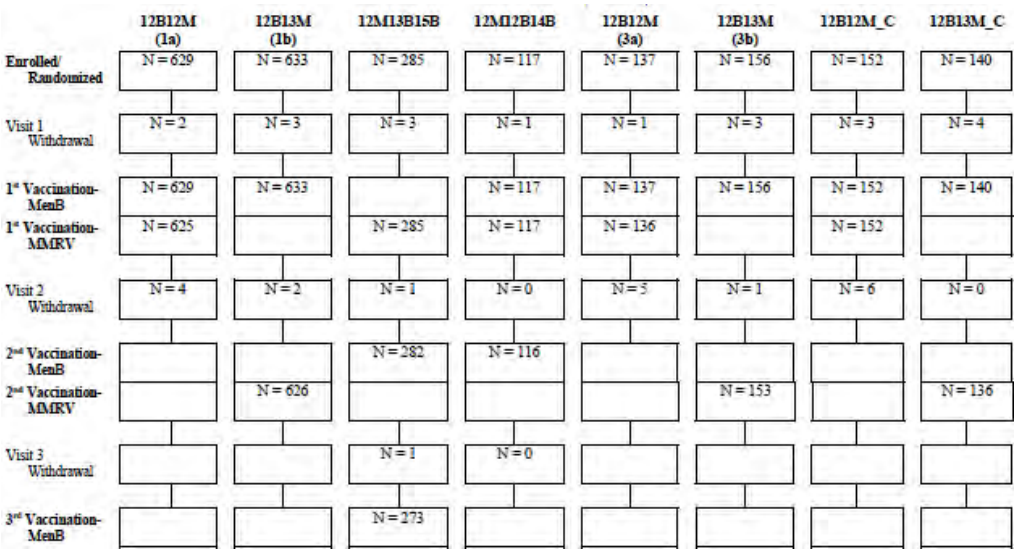
7.1.2.6.9. Participant flow

A total of 2249 subjects were enrolled and 2202 subjects completed the study. Forty seven subjects withdrew due to an AE, withdrawal of consent, inappropriate enrolment, lost to follow-up or protocol deviations/violations (Table 36). No deaths were reported in this study. The study flowchart (Figure 13) shows study terminations and the number of subjects completing the protocol, by vaccine group.

Table 36: Summary of Study Terminations – Enrolled Population in V72P13E1

	12B12M (1a)	12B13M (1b)	12M13B15B	12M12B14B	12B12M (3a)	12B13M (3b)	12B12M_C	12B13M_C	Total
Enrolled	629	633	285	117	137	156	152	140	2249
Completed study	623 (99%)	627 (99%)	274 (96%)	116 (99%)	131 (96%)	152 (97%)	143 (94%)	136 (97%)	2202 (98%)
Completed protocol	623 (99%)	627 (99%)	274 (96%)	116 (99%)	131 (96%)	152 (97%)	143 (94%)	136 (97%)	2202 (98%)
Premature withdrawals	6 (<1%)	6 (<1%)	11 (4%)	1 (<1%)	6 (4%)	4 (3%)	9 (6%)	4 (3%)	47 (2%)
AE	0	1 (<1%)	1 (<1%)	0	0	0	0	0	2 (<1%)
Withdrew consent	3 (<1%)	4 (<1%)	6 (2%)	1 (<1%)	0	0	1 (<1%)	1 (<1%)	16 (<1%)
Lost to follow-up	3 (<1%)	1 (<1%)	1 (<1%)	0	4 (3%)	4 (3%)	8 (5%)	2 (1%)	23 (1%)
Inappropriate enrolment	0	0	0	0	1 (<1%)	0	0	0	1 (<1%)
Protocol deviation/violation	0	0	3 (1%)	0	1 (<1%)	0	0	1 (<1%)	5 (<1%)

Figure 13: Subject Disposition Flowchart in VP13E1



7.1.2.6.10. Major protocol violations/deviations

Major deviations were mostly due to blood draw/ vaccination outside the designated time window or missing a blood draw/vaccination. All subjects with major protocol deviations were analysed for the safety analysis.

7.1.2.6.11. Baseline data

The demographic and other baseline characteristics were balanced across the different vaccination groups. A total of 2249 subjects were enrolled, and 2202 completed the study. A total of 327 subjects were included in the hSBA persistence per protocol (PP) analysis, 424 subjects were included in the hSBA booster PP analysis, 233 subjects were included in the hSBA two-dose PP analysis and 337 subjects were included in the MMRV PP analysis. 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. Except for 41 subjects all of the enrolled subjects met the study entry criteria.

7.1.2.6.12. Results for the primary efficacy outcome

One month after the rMenB+OMV NZ booster vaccination (at 13 months) administered with (group 12B12M(1a)) or without (group 12B13M(1b)) concomitant MMRV vaccination, 100%, 100% and 94%-97% subjects achieved hSBA ≥1:5 against *N meningitidis* serogroup B reference strains 44/76, 5/99 and NZ98/254, respectively. The primary criterion to determine a sufficient immune response (lower limit of the two-sided 95% CI ≥ 75%) was achieved for all three *N meningitidis* serogroup B reference strains.

7.1.2.6.13. Results for other efficacy outcomes

The non-inferiority criterion for antibody responses against MMRV when given with/without rMenB+OMV NZ (i.e., lower limit of the two-sided 95% CI for the difference in responses no greater than -10%) was achieved for the measles, mumps and rubella antigens at the specified cut-off levels. For varicella, 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 gpELISA units/mL (seroprotection), although the difference between the groups was only 2%. It should be noted that subjects had received only one of the two recommended MMRV doses at the time of analysis.

One month after the booster vaccination (at 13 months), the increase in hSBA titres was similar in subjects with or without concomitant MMRV vaccination (GMTs 139 and 119 for strain 44/76; 1503 and 1429 for strain 5/99; 39 and 32 for strain NZ98/254). In subjects, who had

received vaccination with rMenB+OMV NZ concomitantly with routine infant vaccines at 2, 4 and 6 months of age in study V72P13, persistence of bactericidal antibodies at 12 months, as measured by hSBA GMTs, was observed for strain 44/76 and strain 5/99 while for the strain NZ98/254, the hSBA titres returned to the baseline level. However, the percentages of subjects with hSBA ≥ 1:5 remained higher than baseline at 12 months, for all three reference strains. One month after the booster vaccination (at 13 months), the hSBA titres were many-fold higher in subjects receiving a fourth dose of rMenB+OMV NZ than those receiving their first single dose of rMenB+OMV NZ: the ratios for hSBA GMTs at 13 months were 8.84 for strain 44/76, 25 for strain 5/99 and 9.36 for strain NZ98/254. Thus the criteria for demonstrating immunological memory were met for all three strains.

One month after the two-dose schedules, the hSBA titres increased significantly. The increase in hSBA titres for the three reference strains was similar in both 13 and 15 months or 12 and 14 months dose schedules (GMR 217 and 203 for strain 44/76; GMR 560 and 620 for strain 5/99; GMR 43 and 31 for strain NZ98/254 in the respective two dose schedules). A similar response was observed in terms of percentages of subjects with hSBA ≥ 1:5 (100% and 100% for strain 44/76; 100% and 100% for strain 5/99; 100% and 96% for strain NZ98/254 in the respective two-dose schedules).

Overall, the study demonstrated that a 12-months booster produced a more than sufficient immune response in infants primed with a 3-dose primary course, that both 2-dose schedules in naive infants produced a response similar to that seen in the boosted primed infants, and that there was no interference with the responses to MMR. Non-interference of the varicella immune response was demonstrated for seroconversion rate. However, non-inferiority was not met for varicella using the seroprotection cut-off, although the difference in rates between groups was only 2%. As subjects had received only one of the two recommended MMRV doses, his finding is unlikely to be clinically important as the difference in seroprotection rates is minimal.

The second secondary objective was the assessment of the 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, as measured by SBA GMTs and percentage of subjects with SBA titres ≥1:5 at one month after the fourth dose of rMenB+OMV NZ, directed against *N. meningitidis* serogroup B reference strains 44/76, NZ98/254 and 5/99. For strain 5/99 at baseline (at 12 months), the SBA titres were similar (11 and 10, respectively) in the 12B12M (1a) and 12B13M (1b) groups. One month after the booster vaccination (at 13 months), the SBA titres increased to 139 and 119, respectively. The increase in SBA titres was similar in subjects with or without concomitant MMRV vaccination (GMR 13 and 11, respectively). For strain 44/76, at the baseline (at 12 months), the SBA titres were the same (81) in both the 12B12M (1a) and 12B13M (1b) groups. One month after the booster vaccination (at 13 months), the SBA titres increased to, 1503 and 1429 respectively. The increase in SBA titres was similar in subjects with or without concomitant MMRV vaccination (GMR 18 in both groups; for strain NZ98/254, at the baseline (at 12 months), the SBA titres were low and similar (2.07 and 2.21, respectively) in the 12B12M (1a) and 12B13M (1b) groups. One month after the booster vaccination (at 13 months), the SBA titres increased to 39 and 32, respectively. The increase in SBA titres was similar in subjects with or without concomitant MMRV vaccination (GMR over the baseline being 19 and 15, respectively).

> **Comment**: Overall, this large extension study from V72P13E1 demonstrated that a 12-months booster produced a significant immune response in infants primed with a 3-dose primary course, and also that both 2-dose schedules in naïve infants produced a response similar to that seen in the boosted primed infants, and that there was no interference with the responses to MMR. Non-inferiority was not met for varicella using the seroprotection cut-off, although the difference in rates between groups was only 2%. As subjects had received only one of the two recommended MMRV doses, this finding is unlikely to be clinically important as the difference in seroprotection rates is minimal.

7.1.2.7. Study V72P13E2, in infants

7.1.2.7.1. Study design, objectives, locations and dates

V72P13E2 was an extension study of V72P13E1 and enrolled eligible subjects who had participated in the open-label, immunogenicity subset of study V72P13E1. This part of study V72P13E1 was conducted in Finland and Czech Republic. It was conducted as an open-label, multi-centre study and enrolled eligible subjects who participated in the open-label, immunogenicity subset of study V72P13E1 conducted in Finland and Czech Republic. An additional group of naïve subjects, (defined as subjects who have never previously received any meningococcal B vaccine) approximately 24 months of age, were recruited at the same study sites, and received two doses of rMenB+OMV NZ at 24 and 26 months of age. The relationship of subjects in Groups 1a, 1b, 2a to 2b to extension study V72P13E1 and to the original parent study V72P13 is shown in Table 37.

The design was as follows:

Groups 1a and 1b: Both group 1a and 1b received 3 doses of rMenB+OMV NZ and routine vaccines at 2, 4, 6 months of age followed by booster dose of rMenB+OMV NZ at 12 months of age. Group 1a received MMRV at 12 months of age and group 1b received MMRV at 13 months of age. Subjects who were vaccinated with a booster (fourth) dose of rMenB+OMV NZ vaccine at 12 months of age in study V72P13E1 (groups 1a and 1b immunogenicity and safety subjects) Had a blood sample drawn for serological analyses 12 months later (-30/+60 days).

Study treatment arms

Groups 2a and 2b: Group 2a and 2b received routine vaccines at 2, 4, 6 months followed by MMRV at 12 months of age. Group 2a received rMenB+OMV NZ at 13 and 15 months of age and group 2b received rMenB+OMV NZ at 12 and 14 months of age. Subjects who were vaccinated with two catch-up doses of rMenB+OMVNZ vaccine in study V72P13E1 (groups 2a and 2b immunogenicity and safety subjects) had a blood sample drawn for serological analyses 12 months (-30/+60 days) after the second dose. At the same visit, subjects were vaccinated with a booster (third) dose of rMenB+OMV NZ, followed by a blood sample drawn for serological analyses one month later. A third blood sample will be drawn after 6 months of safety follow-up to assess antibody persistence at this later time point.

Group 3: An additional study group consisting of 150 newly recruited naïve. Subjects (defined as subjects who had never received rMenB+OMV NZ or other experimental MenB vaccines), approximately 24 months of age (window: 23-27 months), were enrolled into the study. These subjects served as a comparator for assessing antibody persistence in the above mentioned groups (1a, 1b, 2a, 2b) groups and had a blood sample drawn for serological analyses at entry. These subjects then received two doses of rMenB+OMV NZ two months apart. A second blood sample will be drawn one month after the second dose, and a third blood sample will be obtained after 6 months safety follow-up.

A summary of the study groups, together with the blood sampling and study vaccination schedules are provided in Table 37. The relationships of subjects in groups 1a, 1b, 2a to 2b to extension study V72P13E1 and to the original parent study V72P13 are also shown in this table.

Table 37: Study Design and Group Descriptions in V72P13E2: Assignments and Vaccinations in the Parent Trials V72P13 & V72P13E1

Group	V72P13	V72P13E1	V72P13E2
1a	3 doses rMenB+OMV NZ and routine vaccines at 2, 4, 6 months of age	1 dose rMenB+OMV NZ at 12 months of age; MMRV concomitantly at 12 months of age	Persistence blood draw at 24 months of age
1b	3 doses rMenB+OMV NZ and routine vaccines at 2, 4, 6 months of age	1 dose rMenB+OMV NZ at 12 months of age; MMRV at 13 months of age	Persistence blood draw at 24 months of age
2a	Routine vaccines only at 2, 4, 6 months of age	2 doses rMenB+OMV NZ at 13 and 15 months of age; MMRV at 12 months of age	Persistence blood draw, 1 dose rMenB+OMV NZ, at 27 months of age
2b	Routine vaccines only at 2, 4, 6 months of age	2 doses rMenB+OMV NZ at 12 and 14 months of age; MMRV concomitantly at 12 months of age	Persistence blood draw, 1 dose rMenB+OMV NZ, at 26 months of age
3	NA*	NA*	2 doses rMenB+OMV NZ at 24 and 26 months of age*

*these newly recruited, naïve subjects had never received rMenB+OMV NZ or other experimental MenB vaccines before entry into V72P13E2

7.1.2.7.2. Inclusion and exclusion criteria

Inclusion criteria:

- Healthy children who participated in the immunogenicity part of V72P13E1 and have received their last vaccination 12 months (-30/+60 days) before enrolment in V72P13E2.
- Who received all vaccinations with rMenB+OMV NZ in V72P13 and V72P13E1 according to the protocols.
- Who provided at least the blood sample one month after their fourth dose of rMenB+OMV NZ (groups 1a/1b) or after their second dose of rMenB+OMV NZ (groups 2a/2b) in V72P13E1 according to the protocol.
- For whom parent(s)/legal guardian(s) had given written informed consent after the nature of the study has been explained.
- Available for all the visits scheduled in the study.
- In good health as determined by medical history, physical examination, clinical judgment of the investigator.

Exclusion criteria

Exclusion Criteria for naïve subjects newly enrolled (group 3):

- Subjects whose parent(s)/legal guardian(s) were unwilling or unable to give written informed consent to participate in the study;
- History of any meningococcal B vaccine administration;
- Previous ascertained or suspected disease caused by N. meningitidis;
- Household contact with and/or intimate exposure to an individual with laboratory confirmed *N. meningitidis;*
- History of severe allergic reaction after previous vaccinations or hypersensitivity to any vaccine component;

- Significant acute or chronic infection within the previous 7 days or axillary temperature ≥38°C within the previous day;
- Antibiotics treatment within 6 days prior to enrolment;
- Any serious chronic or progressive disease according to the judgment of the investigator (e.g., neoplasm, diabetes mellitus Type I, cardiac disease, hepatic disease, neurological disease or seizure, either associated with fever or as part of an underlying neurological disorder or syndrome, autoimmune disease, HIV infection or AIDS, or blood dyscrasias or diathesis, signs of cardiac or renal failure or severe malnutrition);
- Known or suspected impairment/alteration of the immune system, immunosuppressive therapy, use of systemic corticosteroids or chronic use of inhaled high-potency corticosteroids within 30 days prior to enrolment (use of low or moderate doses of inhaled steroids is not an exclusion);
- Receipt of blood, blood products and/or plasma derivatives or any parenteral immunoglobulin preparation within 90 days prior to enrolment;
- Receipt of, or intent to immunize with any other vaccine(s) within 30 days prior to enrolment (exception: flu-vaccines should not be administered within 14 days prior to enrolment);
- Participation in another clinical trial within 90 days prior to enrolment or planned for during study;
- Family members and household members of research staff;
- Any condition which, in the opinion of the investigator, might interfere with the evaluation of the study objectives.

7.1.2.7.3. Study treatments

Investigational vaccine (rMenB+OMV NZ) was supplied as a liquid formulation in a prefilled syringe. rMenB+OMV NZ vaccine was given in dose of 0.5mL into the deltoid area of the non-dominant arm or in the antero-lateral area of the right thigh if the deltoid mass was not sufficient.

7.1.2.7.4. Efficacy variables and outcomes

The primary efficacy outcome was:

- Exploration of antibody persistence at one year after a booster (fourth) dose of rMenB+OMV NZ, administered at 12 months of age to toddlers enrolled in study V72P13E1 who previously received a three-dose primary series of rMenB+OMV NZ (administered at 2, 4 and 6 months of age) as infants in the original parent study V72P13.
- Exploration of antibody persistence at one year after two catch-up doses of rMenB+OMV NZ, previously administered to toddlers at either 12 and 14 or 13 and 15 months of age in study V72P13E1.
- Characterization of antibody response to a booster (third) dose of rMenB+OMV NZ administered at one year after two catch-up doses of rMenB+OMV NZ, previously administered to toddlers at either 12 and 14 or 13 and 15 months of age in study V72P13E1.
- Exploration of antibody persistence at 6 months after a booster (third) dose of rMenB+OMV NZ administered one year after two catch-up doses of rMenB+OMV NZ in the second year of life.
- Characterization of antibody response to two catch-up doses of rMenB+OMV NZ administered to naïve (defined as subjects who have never previously received any meningococcal B vaccine) children at 24 and 26 months of age.

- Exploration of antibody persistence at 6 months after two catch-up doses of rMenB+OMV NZ administered to naïve children at 24 and 26 months of age.

7.1.2.7.5. Randomisation and blinding methods

Subjects were assigned to the vaccination groups based on the groups they were assigned to in the parent trial V72P13E1 (groups 1a, 1b, 2a and 2b) or to group 3 in case of naïve subjects.

The trial was conducted as an open-label study.

7.1.2.7.6. Analysis populations

See section 7.1.1.1.6 for definitions.

7.1.2.7.7. Sample size

A maximum number of 240 subjects in group 1a and 250 subjects in group 1b from study V72P13E1 were eligible to participate in this extension study. A maximum number of 210 and 90 subjects in groups 2a and 2b from study V72P13E1, respectively, were eligible to participate in this extension study. These numbers represent the total number of subjects who participated in the immunogenicity and safety cohort of study V72P13E1, which was conducted in Finland and the Czech Republic. A group of 150 newly recruited, naïve subjects, approximately 24 months of age, were concurrently enrolled into the study. These subjects were enrolled in the same study centers in Finland and the Czech Republic. Assuming 10% dropout, there were 135 evaluable subjects in group 3. Power calculations were based on NQuery Advisor 6.01 (Two-group Fisher's Exact Test for equal proportions [unequal N's]).

7.1.2.7.8. Statistical methods

The immunogenicity explorations detailed above were analysed descriptively. As such, no statistical tests were performed. For the immunogenicity endpoints 95% confidence intervals were calculated. The analyses of the immunogenicity results were based on the Intention-to-treat population.

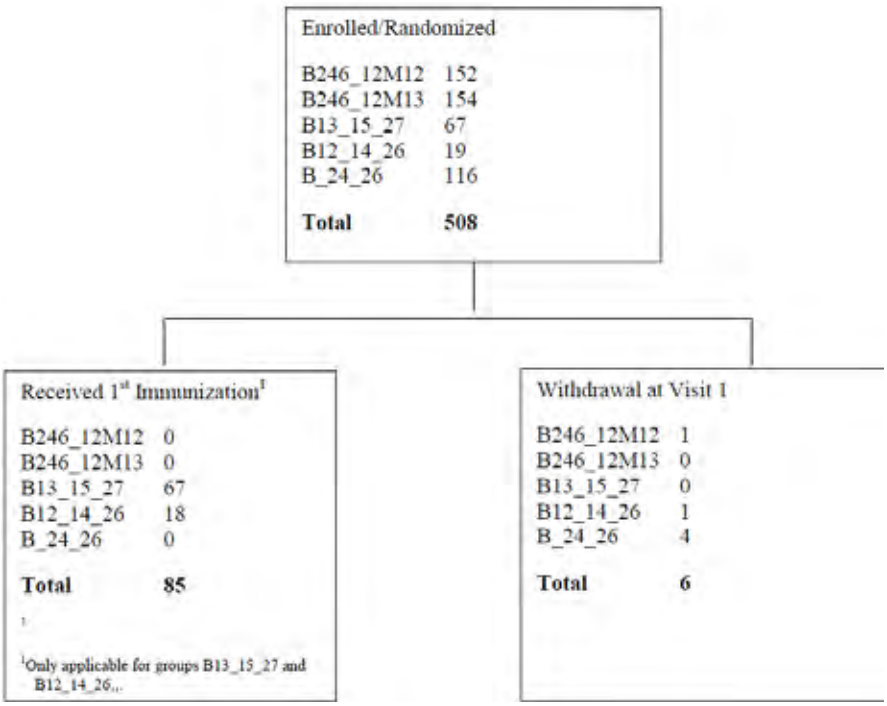
7.1.2.7.9. Participant flow

A total of 508 subjects were enrolled and 305 subjects completed the protocol at the time the interim analysis took place. Six subjects withdrew due to withdrawal of consent (3 subjects) and protocol deviations/violations (3 subjects) (Table 38 and Figure 14).

Table 38: Summary of Study Terminations – Enrolled Population

	B246_12M12	B246_12M13	B13_15_27	B12_14_26	B_24_26
	N=152	N=154	N=67	N=19	N=116
Enrolled	152	154	67	19	116
Ongoing	0	0	67 (100%)	18 (95%)	112 (97%)
Completed protocol	151 (99%)	154 (100%)	0	0	0
Premature withdrawals	1 (<1%)	0	0	1(5%)	4 (3%)
Withdrew consent	0	0	0	1(5%)	2 (2%)
Protocol deviation/violation	1 (<1%)	0	0	0	2 (2%)

Figure 14: Subject Disposition Flowchart



7.1.2.7.10. Major protocol violations/deviations

A total of 32 major protocol deviations were reported. Three subjects received forbidden concomitant medication and 2 subjects received a wrong treatment. One subject did not receive first vaccination and 9 subjects did not meet entry criteria. The major protocol deviations were subjects did not have 1st blood draw (2%), subjects did not meet entry criteria (2%), 1st blood draw outside time window (<1%), subjects did not have 2nd blood draw (<1%), subjects did not receive 1st vaccination (<1%), subjects had taken forbidden medication (<1%), subjects received wrong treatment (<1%), and subjects were too old (<1%).

7.1.2.7.11. Baseline data

The demographic and other baseline characteristics were balanced across the different vaccination groups. A total of 498 subjects were included in the hSBA persistence MITT analysis and 85 subjects were included in the hSBA two-dose catch-up 1 month post booster MITT analysis.

7.1.2.7.12. Results for the primary efficacy outcome

In groups 1a and 1b, antibody persistence was demonstrated one year after a fourth (booster) dose of rMenB+OMV NZ given at 12 months of age to subjects enrolled in study V72P13E1 as measured by hSBA GMTs and percentages of subjects with hSBA ≥1:5. Persistence was much higher for strains 44/76 and 5/99 while for the strain NZ98/254, hSBA titres were less high but still higher than titres of naive subjects at 24 months of age (group 3). For strain M10713, the percentages of subjects with hSBA ≥1:5 at 12 months after the booster vaccination were 32%-40% across Group 1a and Group 1b, and GMTs were 3.61- 4.34. In groups 2a and 2b, twelve months after the two-dose catch-up schedules, antibody persistence as measured by hSBA GMTs and the percentage of subjects with hSBA ≥1:5 were much higher for strains 44/76-SL and 5/99 while for strains NZ98/254 and M10713, hSBA titres were less high but still higher than titres of naive subjects (group 3). One month after the booster vaccine for the two-dose catch up schedule, hSBA titres increased significantly (GMT 369 and 287 for strain 44/76; GMT 3269 and 2599 for strain 5/99; GMT 71 and 89 for strain NZ98/254, GMT 40 and 33 for strain M10713 in the respective two-dose catch-up schedules). Robust hSBA responses were reflected

by high percentages of subjects achieving four fold increases in hSBA titres (100% and 100% for strain 44/76; 99% and 100% for strain 5/99; 97% and 94% for strain NZ98/254 in the respective two-dose catch-up schedules.

Comment: This was an extension study of V72P13E1 for which interim results are submitted with this application (final report pending). Overall, the results of this study demonstrated persistence of bactericidal antibodies at one year after a booster (fourth) dose of rMenB+OMV NZ, administered at 12 months of age, and after two catch-up doses of rMenB+OMV NZ previously administered to toddlers at either 12 and 14 or 13 and 15 months of age. rMenB+OMV NZ was also found to be highly immunogenic when given as a booster (third) dose at one year after a two-dose catch-up schedule in toddlers.

7.1.3. Analyses performed across trials (pooled analyses and meta-analyses)

The V72 series of clinical studies has used the hSBA cut-off of 1:4 (or 1:5 for later studies, following hSBA validation (see section 4.1) Measurements of Immunogenicity) as a surrogate of protection against the three reference strains of N meningitidis group B (44/76, 5/99 and NZ98/254). Table 39 compares results across studies for this protective cut-off against the reference strains for adults and adolescents, and Table 41 and Table 42 compare results across studies for infants and toddlers. These studies used very similar design, methods and evaluations, plus they followed on from each other (as part of the development program).

The immunogenicity data presented in these tables demonstrate that:

- Two vaccinations 1-2 months apart induce adequate immune responses against the reference strains in adolescents 11 to 17 years of age and adults over 18 years of age.
- Two vaccinations six months apart, induce adequate robust immune responses against the reference strains in adolescents 11 to 17 years of age.
- Two vaccinations two months apart, induce adequate robust immune responses against the reference strains in infants 6 to 8 months of age, and toddlers 12 to 23 months of age.
- Three vaccinations one or two months apart, induce adequate robust immune responses against the reference strains in infants 2 months of age at first vaccination.
- A dose in the second year of life after the three-dose vaccination series results in a significant booster response beyond the levels seen after the third vaccination in infants 2 months of age at first vaccination. The booster response is indicative that the three-dose primary series had primed the infants and that immunological memory had been induced.
- Concomitant routine vaccinations co-administered with the three rMenB+OMV NZ vaccinations, given one or two months apart, appear to make no difference to the immune responses against the MenB reference strains in infants 2 months of age at first vaccination.
- Routine vaccinations intercalated at one month after each of the three rMenB+OMV NZ vaccinations, given two months apart, appear to make no difference to the immune responses against the MenB reference strains in infants 2 months of age at first vaccination.

Table 39: Percentage of Subjects with hSBA ≥ 1:4 Against the 3 Reference Strains Across Studies in Adults and Adolescents

Study	Age at enrollment	rMenB+OMV NZ Schedule (months)	Strain	Month 0 Baseline	1-mth Post 1st Vacc	1-mth Post 2nd Vacc	1-mth Post 3rd Vacc
V72P4	Adults 18-50 y	0,2,6	44/76	37	84	100	97
			5/99	37	88	100	100
			NZ98/254	22	80	91	92
V72P5	Adults 18-40 y	0,1,2	44/76	32	-	100	100
			5/99	43	-	100	100
			NZ98/254	18	-	96	93
V72P10	Adolescents 11-17 y	0	44/76	46	92	-	-
			5/99	37	97	-	-
			NZ98/254	37	93	-	-
		0,1	44/76	39	93	100	-
			5/99	30	97	100	-
			NZ98/254	34	94	100	-
		0,2	44/76	44	92	100	-
			5/99	35	96	99	-
			NZ98/254	36	92	100	-
		0,1,2	44/76	46	95	100	100
			5/99	36	97	100	100
			NZ98/254	33	95	100	99
		0,6	44/76	42	92	100	
			5/99	29	97	99	
			NZ98/254	32	90	100	

Table 40: Percentage of Subjects with hSBA ≥ 1:4 or ≥ 1:5a Against the 3 Reference Strains, Across Studies in Infants and Toddlers

Study	Age at enrollment	rMenB+OMV NZ Schedule (months	Strain	(Month 0) Baseline	1-mth Post 2nd Vacc	1-mth Post 3rd Vacc	6-mos Post-3rd Vacc	1-mth Post Booster
V72P9	Infants 6 to 8 mo	0,2,6	44/76	29	100	100	-	-
			5/99	0	100	100	-	-
			NZ98/254	0	95	96	-	-
V72P6	Infants 2 mo	0,2,4, booster at 12 months of age	44/76	11	95	87	68	100
			5/99	14	100	95	88	97
			NZ98/254	9	74	85	36	94
		Vaccinations given, at Age in Months						
V72P12[a]	Infants 2 mo	rMenB+OMV NZ + Routine[b] at 2,4,6	44/76	9	-	99	-	-
			5/99	5	-	99	-	-
			NZ98/254	3	-	79	-	-
		rMenB+OMV NZ at 2,4,6 Routine[b] at 3,5,7	44/76	7	-	99	-	-
			5/99	7	-	99	-	-
			NZ98/254	1	-	87	-	-
		rMenB+OMV NZ + Routine[b] at 2,3,4	44/76	6	-	99	-	-
			5/99	5	-	100	-	-
			NZ98/254	2	-	81	-	-

=Not Applicable

Table 41: Percentage of Subjects with hSBA ≥ 1:5 Against the 3 Reference Strains, Across Studies in Infants and Toddlers

Study	Age at enrollment	Vaccinations given, at Age in Months	Strain	Baseline	1-mth Post-3rd Vacc	6-mos Post-3rd Vacc	1 mth Post Booster or Post 1st rMenB+OMV NZ Vacc in Naive Toddlers	12 mth Post Booster Or 1 mth Post 2nd Vaccination in Naive Toddlers	12 mth post 2nd Vaccination in Naive Toddlers	1 mth post booster in 2-dosed Naive toddlers
V72P13	Infants 2 mo	rMenB +OMV NZ	44/76	3	100	81-82[a]	100[a]	60-64[a]	-	-
V72P13 E1		+ Routine[b] at 2,4,6	5/99	4	100	98-100[a]	100[a]	96-99[a]	-	-
V72P13 E2		booster at 12	NZ98/254	1	84	20-21[a]	94-97[a]	17-18[a]	-	-
		Routine only at 2,4,6	44/76	-	-	5	-	100	74	100
		MMRV[c] at 12	5/99	-	-	1	-	100	97	100
		rMenB+OMV NZ at 13 and 15	NZ98/254	-	-	1	-	100	18	100
		Routine only at 2,4,6	44/76	-	-	3	86	100	56	100
		MMRV[c] at 12	5/99	-	-	1	97	100	94	100
		rMenB+OMV NZ at 12 and 14	NZ98/254	-	-	0	48	94	6	100

* first percentage is for subjects who received booster plus concomitant MMRV at 12 months, the second is for subjects who received booster at 12 months and MMRV at 13 months. bInfanrix Hexa and Prevenar; c Priorix-Tetra. - Not Applicable.

7.2. Evaluator's conclusions on clinical efficacy for active immunization against invasive disease caused by *N. meningitidis* of individuals from 2 months of age and older

The data included in this dossier is complex and expansive but appears to support the following:

- The immune responses to the rMenB+OMV NZ vaccine are sufficient in infants who receive the first vaccination at 2 months of age after three doses given at least one month apart with or without routine vaccines administered concomitantly. It also appears that these vaccines can be given 1 month apart without any change in efficacy. The sufficiency of the immune responses to rMenB+OMV NZ when administered concomitantly with routine vaccines as a three-dose infant primary series at 2, 4 and 6 months of age is supported by the data from V72P13 and V72P12 studies. A non-inferiority approach was used to evaluate the immune responses to rMenB+OMV NZ when administered concomitantly with or without routine vaccines in study V72P12, using predefined noninferiority criteria.
- The immune responses to the vaccine are sufficient in immunologically naïve older infants and toddlers 6 months of age and older after two doses of rMenB+OMV NZ given two months apart. The data from study V72P9 in which a two-dose schedule at 6 to 8 months of age was used, and in immunologically-naive toddlers in study V72P13E1 using a two-dose schedule with or without concomitant vaccines appears to support this.
- The immune responses to a booster dose given to toddlers in their second year of life induce a persistent booster response, either following a three-dose infant primary schedule given one or two months apart starting at 2 months of age, or following a two-dose older, immunologically-naive infant schedule given two months apart starting at 6 months. Adequate immune responses to a booster dose given at 12 months of age with or without concomitant MMRV vaccination, following a 3-dose primary infant series, were shown in study V72P13E1. The immune responses to a rMenB+OMV NZ dose at 12 months of age after a two-dose primary series in naive older infants in study V72P9 was sufficient. Data from study V72P13E2 showed a good response to a booster dose given at one year following a 2-dose catch-up series in toddlers in the second year of life.
- Immune responses were assessed one month following completion of the primary vaccination course in infants (V72P12, V72P13), toddlers (V72P9), adolescents (V72P10)

and adults (V72P4 and V72P5). In the extension studies (V72P13E1 and V72P13E2) the durability of these responses in the infants/toddlers and the effect of booster doses were further studied. Persistence of bactericidal antibodies at 12 months of age (following vaccination at 2, 4 and 6 months) prior to the booster was evaluated in V72P13E1 (as well as one month post-booster). The persistence of antibodies 12 months after the 12-month booster (as well as 12 months after primary two-dose toddler vaccination, was then evaluated in Study V72P13E2.

- Lot to lot consistency of the rMenB+OMV NZ was shown in study V72P13.
- Concomitantly administered routine infant and toddler vaccinations elicit similar immune responses when given with rMenB+OMV NZ vaccine when compared to the same vaccines given alone. This is supported by the data from study V72P12 and study V72P13.
- The response to the first dose of the two-dose series of the four antigens contained in Priorix-Tetra (measles, mumps, rubella and varicella) is non-inferior when given with or without rMenB+OMV NZ (study V72P13E1), using predefined statistical criteria.
- The immune responses to the rMenB+OMV NZ vaccine are sufficient in adolescents 11-17 years of age after two doses, given at least one month apart. This appears to be supported by the results of study V72P10. All available data for subjects in this age group by schedule were combined to increase numbers analysed.
- The immune responses to the rMenB+OMV NZ vaccine appear to be sufficient in adults 18-50 years of age after two doses, given at least one month apart. This was supported by the results of studies V72P5 and V72P4 (small studies).
- There is no specific data for efficacy in children aged 2-10 years of age.

8. Clinical safety

8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

For all the studies discussed in Section 7 above, safety and tolerability were co-primary objectives (with immunogenicity). The design, methods and patient flow for all these studies is described in Section 7. All subjects receiving at least one injection and providing post-baseline safety data were included in the safety and tolerability analyses. The safety data in adolescents comes from study V72P10 which compared rMenB+OMV NZ vaccine to placebo in various schedule combinations. The safety of rMenB+OMV NZ vaccine in adults was evaluated in studies V72P4 and V72P5. In infants [vaccine safety was assessed] beginning at 2 months of age as a three-dose schedule, given at least one month apart with or without concomitantly administered routine childhood vaccines. Safety was evaluated in both studies V72P12 and V72P13. The safety and tolerability of rMenB+OMV NZ administered to vaccine-naïve older infants and toddlers beginning at 6 months of age in a two-dose schedule given two months apart was evaluated in vaccine-naïve toddlers in study V72P13E1 in a two-dose schedule at 12 and 14 months of age or 13 and 15 months of age with or without Priorix-Tetra vaccine. rMenB+OMV NZ vaccine was evaluated in vaccine naïve older infants in study V72P9 in a two-dose schedule given two months apart starting at 6 to 8 months of age. The safety and tolerability profile when given as a booster dose administered to toddlers in their second year of life following a three-dose infant primary series, or at one year following a two-dose schedule at 12 and 14 months of age or 13 and 15 months of age in vaccine naïve toddlers, or at the age of 12 months in older infants given a primary series of two doses two months apart beginning at 6 months of age was assessed in extension study and Extension study V72P13E2 provides safety

data for a booster dose of rMenB+OMV NZ administered at one year after two doses of rMenB+OMV NZ, previously administered to toddlers at either 12 and 14 or 13 and 15 months of age in study V72P13E1. Study V72P9 provides safety data for a booster dose of rMenB+OMV NZ vaccine administered at 12 months of age after a two-dose primary schedule in vaccine naive older infants starting at 6 to 8 months of age at enrolment. The number of participants available for safety data in the different studies is summarised in Table 42 (primary vaccination) and Table 43 (booster vaccination).

Table 42: Overview of Clinical Studies Included to Support rMenB+OMV NZ Vaccine Safety of Infants (Primary Series) and Adolescents and Adults, 2 Months of Age and Older

Age groups Study Number (Phase)	Study Design	Age at enrollment	Schedule	Number in the Safety Population [a]		Concomitant Routine Vaccines
				rMenB+ OMV NZ	Control	
Adolescents and Adults						
V72P4 (Phase 2)	Open-label, multi-center, safety, and immunogenicity study in healthy (at-risk) adults	18-50 years	0-2-6-month schedule with 2-months safety follow-up	53	None	None
V72P5 (Phase 1)	Observer blind, single-center, randomized, safety, and immunogenicity study in healthy adults	18-40 years	0-1-2-month schedule with 6-months safety follow-up	28	None	None
V72P10 (Phase 2b/3)	Observer-blind, multi-center, randomized controlled, safety, and immunogenicity study in healthy adolescents with various schedules	11-17 years	0; 0-1; 0-2; 0-6; 0-1-2; 0-1-6; 0-2-6-month schedules with 6-months safety follow-up [b]	1631	None (Placebo)	None
Total				1712	None	
Infants and Toddlers						
V72P6 (Phase 2)	Open-label, multi-center, randomized, controlled, safety, and immunogenicity study in healthy infants with various schedules (including a booster dose)	2 months	2-4-6-month schedule with a booster dose at 12 months of age with 6-months safety follow-up	50	49 (Routine)	Pediacel, Prevenar
		12 months	1 dose at 12 months of age with 6-months safety follow-up	24	None	Menitorix
V72P9 (Phase 2)	Single-blind, single-center, randomized, safety, and immunogenicity in healthy infants (includes a booster dose)	6-8 months	6-8-month schedule with a booster dose at 12 months and includes a 6-months safety follow-up	30	None	None
V72P12 (Phase 2b)	Open-label, parallel-group, multi-center, randomized, safety, and immunogenicity in healthy infants with various schedules	2 months	2-4-6 and 2-3-4-month schedule with 6-months safety follow-up	1570	312 (Routine)	InfanrixHexa and Prevenar
V72P13 (Phase 3)	Partially-blinded, multi-center, randomized, controlled, safety, and immunogenicity, lot-to-lot consistency in healthy infants	2 months	2-4-6-month schedule with 6-months safety follow-up	2480	1149 (Routine or MenC conjugate with routine)	InfanrixHexa and Prevenar
V72P13E1 (Phase 3)	Open-label, multi-center, extension study of V72P13	12 months	1 dose in vaccine naive toddlers 12 months of age for original control group in V72P13 with 6-months safety follow-up	291	None	Subset with Priorix-Tetra
		12-13 months	2 doses in vaccine naive toddlers 12 or 13 months of age for original control group in V72P13 with 6-months safety follow-up	401[1]	None	Subset with Priorix-Tetra
Total				4846	1510	

Table 43: Overview of Clinical Studies Included to Support rMenB+OMV NZ Safety (Booster Vaccination)

Study Number (Phase)	Study Design	Age at enrollment	Schedule	Number in the Safety Population		Concomitant Routine Vaccines
				rMenB+OMV NZ	Control	
V72P6 (Phase 2)	Open-label, multi-center, randomized, controlled, safety, and immunogenicity study in healthy infants with various schedules (including a booster dose)	12 months	Booster at 12 months of age with 6-months safety follow-up	48[a]	None	Menitorix
V72P9 (Phase 2)	Single-blind, single-center, randomized, safety, and immunogenicity in healthy infants (includes a booster dose)	12 months	Booster at 12 months of age with 6-months safety follow-up	27[b]	None	None
V72P13E1 (Phase 3)	Open-label, multi-center, extension study of V72P13	12 months	Booster at 12 months of age with 6-months safety follow-up	1555	None	Priorix-Tetra
V72P13E2 (Phase 3)	Open-label, multi-center, extension study of V72P13E1	24 months	Booster dose given one year after 2 doses given to vaccine naive toddlers in V72P13E1 – 30 day safety data	85	None	None
Total				1715	0	

8.1.1. Pivotal efficacy studies

In these studies, specific data on local and systemic reactions and adverse events were collected as shown in Table 44 and detailed beneath.

Table 44: Safety assessments in all studies

Safety Measurements	Duration
Signs or symptoms of anaphylaxis; Immediate local and systemic reactions	30 minutes after each vaccination
Body Temperature[a], Solicited Local[b] and systemic[c] reactions, Quality of life parameter[d], All Adverse Events[e], All medications[f]	For 7 days after each vaccination
Serious Adverse Events, Medically attended adverse events, Adverse Events leading to premature withdrawal from the study, Fever and solicited local/systemic reaction persisting beyond Day 7, All medications for treatment of adverse events recorded in this period, All vaccinations	From Day 8 after each vaccination to next vaccination or to 30 days after last vaccination
Serious Adverse Events, Medically attended adverse events, Adverse Events leading to premature withdrawal from the study, All medications for treatment of adverse events recorded in this period, All vaccinations	From 31 days after last vaccination to the last visit (end of study)

a: Fever, medically attended fever; Prophylactic/therapeutic use of analgesics/antipyretics; Name of analgesics/antipyretics. b: injection site pain, erythema, swelling, induration. All recorded daily c: Nausea, malaise, myalgia, arthralgia, headache. d: stayed at home due to reaction. e: including medically attended adverse events, adverse events leading to premature withdrawal from the study and serious adverse events; f: with the exception of minerals, supplements, vitamins.

8.1.1.1. General adverse events

The severity of the AEs was determined by the investigators as follows:

Mild: No limitation of normal daily activities;

Moderate: Some limitation of normal daily activities;

Severe: Unable to perform normal daily activities.

The relationship of the study vaccine to an AE was determined by the investigator and assessed as:

Not Related: The AE is not related if exposure to the investigational vaccine has not occurred, or the occurrence of the AE is not reasonably related in time, or the AE is considered unlikely to be related to use of the investigational vaccine, i.e. there are no facts (evidence) or arguments to suggest a causal relationship.

Possibly Related: The administration of the investigational vaccine and an AE are considered reasonably related in time and the AE could be explained by causes other than exposure to the investigational vaccine.

Probably Related: Exposure to the investigational vaccine and an AE are reasonably related in time and the investigational vaccine is more likely than other causes to be responsible for the AE, or is the most likely cause of the AE.

8.1.1.1.1. Local and systemic reactions and other indicators of reactogenicity

While conforming to the definition of an AE, selected reactions that occurred within 6 days after the day of injection were used as indicators of reactogenicity. As such, they were assumed to be at least possibly related to the administration of the study vaccine and were recorded as a "Local and Systemic Reactions" rather than "Adverse Events". If a local and systemic reaction continued beyond day 7, it was then recorded as an "Adverse Event" and monitored accordingly.

The selected reactions, or other indicators of reactogenicity, were:

Local Reactions: Tenderness, erythema, swelling and induration

Systemic Reactions: Change in eating habits, sleepiness, unusual crying, vomiting, diarrhoea, and irritability, rash.

Other Indicators of Reactogenicity: Body temperature (from which fever was derived when measured axillary temperature was ≥38.0°C), use of analgesic/antipyretics.

Information on the gradings of these local and systemic adverse events for infants/toddlers and adolescents was provided.

8.1.1.2. Serious adverse events

A SAE was defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (i.e. the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically might have caused death if it were more severe
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e. the event causes a substantial disruption of a person's ability to conduct normal life functions)
- Results in a congenital anomaly/birth defect
- Requires intervention to prevent permanent impairment or damage
- Is an important and significant medical event that may not be immediately life threatening or resulting in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the patient/subject or may require intervention to prevent one of the other outcomes listed above.

8.1.1.3. Clinical laboratory tests

Apart from testing for immunogenicity, clinical laboratory tests were not required by the protocols except in V72P5. Abnormalities in clinical laboratory tests, if any were observed in the course of routine medical care, should be considered clinically significant by the investigators and recorded as "Adverse Events", when applicable.

The assessment of safety was based on the recommendation of the New Vaccines guidelines (CPMP/VWP/164653/2005). Overall, safety measures included:

- Solicited AEs (i.e., local and systemic reactions and other indicators of reactogenicity (e.g., use of analgesic/antipyretic medication) on the day of vaccination (day 1) and each of the following 6 days (days 2-7) in all nine studies (V72P4, V72P5, V72P6, 72P9, V72P10, V72P12, V72P13, V72P13E1, V72P13E2). Medically attended fever [fever was defined as rectal temperature ≥38.5ºC or axillary temperature ≥38°C]) was captured as a solicited systemic reaction in phase 2b and phase 3 studies (V72P10, V72P12, V72P13, V72P13E1, V72P13E2).
- Unsolicited AEs (and related concomitant medications), as defined by the International Conference on Harmonization of Technical Requirements for Registrations of Pharmaceuticals for Human Use, ICH E2A, collected as predefined in the respective study protocols. For all studies, all unsolicited AEs were collected within the first 7 days after each vaccination. All SAEs (including medically significant AEs) were collected throughout the study until the end of the follow-up period. Medically attended AEs and AEs leading to

premature withdrawal were collected throughout the study period for all phase 2b and phase 3 studies, and to 30 days after each vaccination in phase 2 studies.

- Additionally, clinical laboratory data (serum chemistry, immunology, coagulation, urinalysis, and haematology) in study V72P5 were collected at baseline and during the study.

In all the studies above, safety was a co-primary outcome.

8.1.2. Dose-response and non-pivotal efficacy studies

Discussed below.

8.1.3. Other studies evaluable for safety only

N/A

8.2. Pivotal studies that assessed safety as a primary outcome

All the immunogenicity studies assessed safety as a co-primary outcome.

8.3. Patient exposure

The total number of subjects exposed to at least one dose of the rMenB+OMV NZ vaccine was 6555 subjects (from 2 months of age), including 4843 infants and toddlers, 1631 adolescents (11 to 17 years of age) see Table 46, and 81 adults (18 to 50 years of age), see Tables 45 and 46. Of the subjects who received the primary infant series of rMenB+OMV NZ, 1630 received a booster dose in the second year of life (Table 47). Of the subjects who received the 2-dose catch-up schedule in the second year of life, 85 received a booster dose 12 months after the second dose. The safety data in the pivotal studies will be described individually and the others amalgamated.

Table 45: Extent of Exposure to rMenB+OMV NZ and Control Vaccines, by Study, by Vaccination, Primary Infant or Toddler Series

Study	Vaccines Administered	Total Subjects Who Received :		
		Injection 1	Injection 2	Injection 3
V72P6	**rMenB+OMV NZ**	**50**	**48 (96%)**	**48 (96%)**
	Routine	49	49 (100%)	49 (100%)
	Routine → **rMenB+OMV NZ**[a]	**23**	NA	NA
V72P9	**rMenB+OMV NZ**	**30**	**28 (100%)**	NA
V72P12	**B+R246**[b]	**625**	**611 (98%)**	**603 (96%)**
	B246[c]_R357[d]	**627**	**607 (97%)**	**602 (96%)**
		612	604 (96%)	598 (95%)
	B+R234[e]	**318**	**312 (98%)**	**310 (97%)**
	R234[f]	312	306 (98%)	304 (97%)
V72P13	**rMenB+OMV NZ**[g] (lot 1)	**832**	**827 (99%)**	**811 (97%)**
	rMenB+OMV NZ[g] (lot 2)	**828**	**810 (98%)**	**801 (97%)**
	rMenB+OMV NZ[g] (lot 3)	**819**	**804 (98%)**	**799 (98%)**
	Routine[h]	659	654 (99%)	652 (99%)
	MenC+Routine[i]	490	476 (97%)	465 (95%)
		490	479 (98%)	472 (96%)
V72P13E1	12M**13B15B**[j]	285[k]	**282 (99%)**	**277 (97%)**
	12M**12B14B**[l]	**117**	**116 (99%)**	117 (100%)[m]
	12B12M_C[n]	**152**	NA	NA
	12B13M_C[o]	**140**	136 (97%)[p]	NA
Total		7458	7149 (96%)	6908 (93%)

Bold for subjects who received rMenB+OMV NZ; a rMenB+OMV NZ at month 12 only; b rMenB+OMV NZ and routine vaccines (InfanrixHexa and Prevenar) were administered concomitantly at 2, 4, and 6 months of age; c rMenB+OMV NZ was administered at 2, 4, and 6 months of age and d routine vaccines were administered at 3, 5, 7 months of age; e rMenB+OMV NZ and routine vaccines were administered concomitantly at 2, 3, and 4 months of age; f routine vaccines were administered at 2, 3, and 4 months of age; g rMenB+OMV NZ and routine vaccines were administered concomitantly at 2, 4, and 6 months of age; h routine vaccines were administered at 2, 4, and 6 months

of age; i MenC and routine vaccines were administered concomitantly at 2, 4, and 6 months of age; j Priorix-Tetra was administered at 12 months of age and rMenB+OMV NZ was administered at 13 and 15 months of age; k only Priorix-Tetra was administered at month 12; l Priorix-Tetra was administered at 12 months of age and rMenB+OMV NZ was administered at 12 and 14 months of age; m only Priorix-Tetra was administered at month 12; n Priorix- Tetra and rMenB+OMV NZ were administered concomitantly at 12 months of age; o rMenB+OMV NZ was administered at 12 months of age and Priorix-Tetra was administered at 13 months of age; p only Priorix- Tetra was administered at 13 months of age.

Table 46: Extent of Exposure to rMenB+OMV NZ Vaccine and Control Vaccines, by Age, by Study, by Vaccination, in Adolescents and Adults

Age Group Study	Vaccines Administered	Total Subjects Who Received :				
		Injection 1	Injection 2	Injection 3	Injection 4*	
11 to 17 years of age						
V72P10	rMenB0[a]	375 (100%)	351 (94%)	343 (91%)	rMenB06[f]	114 (89%)
					rMenB0[a]	212 (86%)
	rMenB01[b]	375 (100%)	356 (95%)	350 (93%)	rMenB016[g]	112 (88%)
					rMenB01[b]	225 (91%)
	rMenB02[c]	380 (100%)	347 (91%)	341 (90%)	rMenB026[h]	111 (87%)
					rMenB02[c]	222 (86%)
	rMenB012[d]	373 (100%)	342 (92%)	332 (89%)	rMenB012[d]	316 (85%)
	Placebo[e]	128 (100%)	124 (97%)	121 (95%)	rMenB6[i]	119 (93%)
18 to 50 years of age						
V72P4	rMenB+OMV NZ	53 (100%)	52 (98%)	50 (94%)	NA	NA
V72P5	rMenB+OMV NZ	28 (100%)	28 (100%)	28 (100%)	NA	NA

a rMenB0=1 dose of the rMenB+OMV NZ vaccine administered at month 0 and placebo administered at months 1, 2 and 6; b rMenB01=2 doses of the rMenB+OMV NZ vaccine administered at months 0 and 1 and placebo administered at months 2 and 6; c rMenB02=2 doses of the rMenB+OMV NZ vaccine administered at months 0 and 2 and placebo administered at months 1 and 6; d rMenB012=3 doses of the rMenB+OMV NZ vaccine administered at months 0, 1 and 2 and placebo at month 6; e Placebo administered at months 0, 1 and 2; f rMenB06=1 dose of the rMenB+OMV NZ vaccine administered at months 0 and 6, placebo administered at months 1 and 2; g rMenB016=3 doses of the rMenB+OMV NZ vaccine administered at months 0, 1 and 6 and placebo administered at month 2; h rMenB026=3 doses of the rMenB+OMV NZ vaccine administered at months 0, 2 and 6 and placebo administered at month 1; i rMenB6= Placebo administered at months 0, 1 and 2 and 1 dose of the rMenB+OMV NZ vaccine administered at month 6.

Table 47: Extent of Exposure to rMenB+OMV NZ Vaccine, by Study, Booster Dose

Study	Vaccines Administered	Subjects Exposed to Booster (4th or 3rd dose [N])
V72P6	rMenB+OMV NZ	48
V72P9	rMenB+OMV NZ	27
V72P13E1	12B12M[a]	1262
	12B13M[b]	293
V72P13E2	B13_15_27	67
	B12_14_26	18
Total		1715

8.4. Adverse events

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

8.4.1.1. Pivotal studies

8.4.1.1.1. V72P13

A total of 3630 infants were enrolled, 3629 were included in the safety population, and 2480 were included in the rMenB+OMV NZ safety population. One part of this study was open-label, with a control group receiving routine infant vaccines only. A second part of the study was observer-blinded: the inclusion of a group receiving Menjugate as well as the routine vaccination (the MenC+Routine group) allowed blinding of the subject's parents/caretakers, as well as the study staff who evaluated the subjects. A comparison of all three groups receiving rMenB+OMV NZ with both control groups (the Routine and the MenC+Routine groups) was also conducted. Of a total of 3630 enrolled subjects, 3629 received at least one vaccination and were included in the safety analysis (Table 48).

Table 48: Overview of Safety Populations in V72P13

	rMenB lot1 N=833	rMenB lot2 N=828	rMenB lot3 N=820	Routine N=659	MenC+Routine N=490	Total N=3630
Population:						
Enrolled	833 (100%)	828 (100%)	820 (100%)	659 (100%)	490 (100%)	3630 (100%)
Vaccinated	832 (100%)	828 (100%)	820 (100%)	659 (100%)	490 (100%)	3629 (100%)
Safety	832 (100%)	828 (100%)	820 (100%)	659 (100%)	490 (100%)	3629 (100%)
Safety Open Label	661 (79%)	654 (79%)	652 (80%)	659 (100%)	0	2626 (72%)
Safety Observer Blind	164 (20%)	168 (20%)	161 (20%)	0	470 (96%)*	963 (27%)

*40 subjects were excluded from the observer-blind population due to unblinding issues. Safety Population N=3629. One subject did not provide local and systemic reaction data and 3 subjects did not provide any AE data, N=3626

Almost all subjects (87%-99%) had at least one reported local or systemic reaction. Local reactions to the three rMenB+OMV NZ lots were reported by 86 to 90% of subjects, and were higher than those in the MenC+Routine group (70% to 79%), which in turn were higher than those in the Routine group (71% to 72%). The most commonly reported local reaction after vaccination with rMenB+OMV NZ was tenderness, reported for up to 70% of subjects, followed by erythema (up to 64%), induration (up to 56%) and swelling (up to 32%). Systemic reactions were reported more frequently in subjects given rMenB+OMV NZ concomitantly with Infanrix Hexa and Prevenar (88% to 89%) than in those given MenC concomitantly with the routine vaccines (72% to 83%) and in those given the routine vaccines only (71% to 84). The most commonly reported systemic reaction was irritability, recorded for up to 83% of subjects receiving rMenB+OMV NZ, followed by sleepiness (up to 75%) and unusual crying (up to 70%). Fever (≥ 38.5°C rectal) was reported for up to 58% of subjects after receiving rMenB+OMV NZ, compared with up to 26% after routine vaccinations only, and up to 31% after routine vaccinations plus MenC. Fever ≥ 40°C was reported for up to 1% of subjects in both the rMenB All group (i.e., the combined data for the 3 lots) and the Routine group after any vaccination. Percentages of subjects with medically attended fever after any vaccination were 1.42% for the rMenB total group and 1.82% for the Routine group in the open label part of the study. In the observer-blind subset the percentages were 5.27% for the rMenB All group and 2.77% for the MenC+Routine group.

Overall rates of Serious AEs were similar among groups: 8% for rMenB+OMV NZ concomitantly with routine, 8% for Routine and 6% for the MenC plus Routine group. Most SAEs were reported after any vaccination. Suspected febrile and non-febrile seizures were reported for 6 and 9 subjects, respectively. Thirteen of the events were reported as SAEs and two as non-serious. Two cases occurred in control subjects vaccinated with MenC with routine vaccines or routine vaccines alone, while 13 occurred in recipients of MenB+OMV NZ with routine vaccines.

Most of the cases were considered unrelated to vaccination and occurred late after vaccination; however, 2 cases of febrile seizures and 2 cases of non-febrile seizures were considered at least possibly related to vaccination with rMenB+OMV NZ plus routine vaccines. The 2 cases of non-febrile seizure were reported as transient, non-serious adverse events of mild or moderate severity. One of the febrile seizures was reported as a complex febrile seizure in a subject at high risk for seizure, as the child had significant underlying pathology with neurological abnormalities and developmental delay. Two subjects receiving rMenB+OMV NZ experienced febrile seizures within 2 days of vaccination. Four cases of Kawasaki disease were reported, 3 cases in subjects receiving rMenB+OMV NZ concomitantly with routine infant vaccinations, and 1 case in a subject receiving MenC concomitantly with routine vaccinations. However, one of the cases occurred 3 weeks after vaccination with rMenB+OMV NZ with routine vaccines and, as such, the case was upgraded to possibly-related. The others were judged as not related to study vaccination by the investigators.

8.4.1.1.2. VP72P10

A total of 1631 adolescents 11 to 17 years of age were enrolled and included in the safety set, and 1503 were vaccinated with rMenB+OMV NZ up to visit 4. All 1631 subjects were vaccinated with rMenB+OMV NZ after visit 4. In general the safety and tolerability profile was similar across the 1, 2 and 3 dose schedules of the rMenB+OMV NZ vaccine: the incidence and severity of AEs were comparable after each dose. A majority of subjects reported local or systemic reactions within 7-days after each vaccination (Table 49). Most local and systemic reactions were transient and mild or moderate in severity. The most commonly reported local reaction was pain, reported by a majority of subjects after each vaccination in both the rMenB+OMV NZ and placebo groups. Other common reactions were erythema, swelling and induration. There was a decrease in the percentage of subjects reporting local and systemic reactions with subsequent vaccinations (Table 49). The most commonly reported systemic reactions were malaise, myalgia and headache after each vaccination. Other (unsolicited) AEs were also recorded during the 7 day observation period after each vaccination, and these mostly belonged to the SOCs of 'General disorders and administration site conditions' and 'Infections and infestations. The commonly reported AEs were injection site reactions such as pain, induration and swelling. Less than 50% of these AEs were assessed to be at least possibly related to the study vaccination: most occurred within 1 week after each vaccination and most were injection site reactions.

Table 49: Number (%) of Subjects Aged 11 to 17 Years with at Least One Reactogenicity Sign/AE, in Days 1 to 7 after Each Vaccination - Safety Set

Number (%) of Subjects With Solicited Reactions					
	rMenB0	rMenB01	rMenB02	rMenB012	Placebo
	N=375	N=375	N=380	N=373	N=128
Injection: 1					
Any[b]	353(94%)	356(95%)	352(93%)	349(94%)	118(92%)
Local	350(93%)	351(94%)	348(92%)	341(91%)	114(89%)
Systemic	285(76%)	296(79%)	286(75%)	278(75%)	90(70%)
Other	159(42%)	152(41%)	153(40%)	150(40%)	29(23%)
All other AEs[a]	67(18%)	67(18%)	79(21%)	69(18%)	17(13%)
Injection: 2					
	N=351	N=356	N=347	N=342	N=124
Any	258 (74%)	320 (90%)	271 (78%)	312 (91%)	104 (84%)
Local	238 (68%)	315 (88%)	252 (73%)	306 (89%)	95 (77%)
Systemic	177 (50%)	250 (70%)	181 (52%)	244 (71%)	79 (64%)
Other	73 (21%)	95 (27%)	63 (18%)	121 (35%)	18 (15%)
All other AEs	38(11%)	48(13%)	36(10%)	37(11%)	11(9%)
Injection: 3					
	N=343	N=350	N=341	N=332	N=121
Any	250 (73%)	230 (66%)	306 (90%)	289 (87%)	94 (78%)
Local	231 (67%)	213 (61%)	296 (87%)	278 (84%)	87 (72%)
Systemic	148 (43%)	146 (42%)	222 (65%)	221 (67%)	64 (53%)
Other	47 (14%)	54 (15%)	100 (29%)	102 (31%)	17 (14%)
All other AE	20(6%)	24(7%)	37(11%)	42(13%)	10(8%)

Up to visit 4, ten subjects reported SAEs, all being assessed as unrelated to the study vaccines. All SAEs were moderate to severe in intensity and all subjects recovered within the study period. One subject withdrew from the study prematurely due to convulsions experienced two minutes after the first vaccination. The condition was transient and was assessed to be unrelated to study vaccine (the subject had a paternal family history of epilepsy). Up to visit 7, 35 subjects reported SAEs. SAEs in two subjects were assessed to be possibly or probably related to the study vaccination. Most of the SAEs were moderate to severe in intensity and most of the subjects recovered within the study period (Table 50). SAEs were rare and reported by not more than 1% of the subjects across vaccine groups; none of these were assessed to be related to the study vaccination (Table 50). One subject withdrew from the study due an SAE; the AE was assessed to be unrelated to the study vaccination.

Table 50: Number (%) of Subjects Aged 11 to 17 Years Reporting Other AEs, After Any Vaccination - Safety Population

	Number (%) of Subjects with Adverse Events				
	rMenB0	rMenB01	rMenB02	rMenB012	Placebo
	N=375	N=375	N=380	N=373	N=128
Any AEs	147 (39%)	160 (43%)	173 (46%)	161 (43%)	57 (45%)
At least possibly related AEs	49 (13%)	63 (17%)	61 (16%)	67 (18%)	15 (12%)
Serious AEs	1 (<1%)	0	4 (1%)	4 (1%)	1 (1%)
At least possibly related SAEs	0	0	0	0	0
AEs leading to discontinuation	1 (<1%)	0	0	0	0

Ten subjects reported AEs that were assessed to be 'serious'. All the subjects recovered within the observation period and none of these AEs were considered to be related to the study

vaccination. The majority of the SAEs were Infections or infestations (Table 51) and most of the infections and infestations were moderate in severity.

Table 51: Listing Of Serious Adverse Events, By Vaccine Group

Preferred Term	Onset (Study Day)	Duration (days)	Severity	Outcome	Hospitalization	Relatedness
Meningitis Bacterial	82	8	Sev	Recovered	Yes	None
Appendicitis	72	3	Mod	Recovered	Yes	None
Convulsion	1	<1	Sev	Recovered	Yes	None
Drug Toxicity	23	2	Sev	Recovered	Yes	None
Asthmatic Crisis	86	2	Mod	Recovered	Yes	None
Appendicitis	73	2	Sev	Recovered	Yes	None
Appendicitis	92	<1	Sev	Recovered	Yes	None
Urticaria	61	2	Mod	Recovered	No	None
Appendicitis	95	2	Mod	Recovered	Yes	None
Shigella Infection	47	2	Mod	Recovered	Yes	None

Table 51 has been amended from the original to redact patient identifiers

8.4.1.2. Other studies

8.4.1.2.1. Infants and toddlers

V2P13E1 was an extension study of V72P13, in subjects who completed the parent study V72P13. The safety objectives of this extension study included the following evaluations: 1) safety and tolerability of a fourth (booster) dose of rMenB+OMV NZ at 12 months of age administered with and without Priorix-Tetra; 2) safety and tolerability of a two-dose schedule of the rMenB+OMV NZ vaccine in toddlers starting at 12 or at 13 months of age; and 3) safety and tolerability of a single dose of the rMenB+OMV NZ vaccine in toddlers at 12 months of age. All subjects were followed for safety throughout the study.

Safety data were obtained for 2246 of the 2249 enrolled subjects who received at least one vaccination with rMenB+OMV NZ. The majority of the subjects (94%-97%) experienced solicited local and/or systemic reactions within 7 days after vaccination with rMenB+OMV NZ; Most of the local and systemic reactions occurred within the first three days of vaccination. These reactions were transient with few continuing past the day 7 observation period. Assessed on study days 1-7 the percentages of subjects with solicited local and systemic reactions after rMenB+OMV NZ vaccination, were similar between the subjects who were administered the booster rMenB+OMV NZ vaccination at 12 months of age (95%-97%) and the subjects who received the two-dose vaccinations (95%-97%).

Assessed on study days 1-7 the most common local reactions after rMenB+OMV NZ vaccination were tenderness (up to 71%) and erythema (up to 68%). The most common systemic reaction was irritability (up to 73%). Assessed on study days 1-7 the percentages of subjects experiencing solicited local and/or systemic reactions after Priorix-Tetra vaccination, were higher when Priorix-Tetra was given concomitantly with rMenB+OMV NZ (91%-95%) as compared with Priorix-Tetra given alone (81%). Across all vaccination groups, the majority of reactions after Priorix-Tetra vaccination were systemic in nature (range 88%-91% in concomitant vaccination groups, 68% in the group 12M13B15B). Assessed on study days 8-28, the percentages of subjects with solicited reactions after Priorix-Tetra vaccination were 47%-59% across the vaccination groups with no higher reactogenicity with concomitant Priorix-Tetra vaccination with rMenB+OMV. Assessed on study days 1-4, fever appeared to be largely due to the rMenB+OMV NZ vaccination and assessed on study days 5-28 fever appeared to be largely due to the vaccination. Assessed on study days 1-4, the percentage of subjects reporting fever after a dose of rMenB+OMV NZ given alone (either as a fourth (booster) dose at 12 months or as part of the two-dose schedules starting at 12 or 13 months) ranged from 39% to 54%. The percentage of subjects reporting fever from Day 1-4 was similar for rMenB+OMV NZ given

concomitantly with Priorix-Tetra (37%-50%) suggesting that Priorix-Tetra vaccination contributed little to the fever rates from Day 1-4. This was supported by only 8% of subjects presenting with fever from Day 1-4 with Priorix-Tetra given alone at 12 months of age. In contrast, during the 5-28 day period fever was mainly contributed to by Priorix-Tetra vaccination, with 53% of subjects reporting fever during this period following Priorix-Tetra vaccination alone, and a similar percentage of subjects reporting fever (44%-48%) when Priorix-Tetra was co-administered with rMenB+OMV NZ. When rMenB+OMV NZ was given concomitantly with Priorix-Tetra, the fever rates showed a trend towards a sum effect of the two vaccinations i.e. fever reported during the 1-4 day period as well as during the 5-28 day period after the vaccinations. The fever associated with rMenB+OMV NZ was of limited duration with the majority resolving within 2 days. Very few (0- 1%) subjects had fever ≥40°C. The majority of fever was of mild to moderate in intensity throughout.

Overall, the groups with rMenB+OMV NZ and Priorix-Tetra concomitant vaccinations reported higher percentages of AEs (54%-74% all and 28%-33% at least possibly related AEs in groups 12B12M, 12M12B14B, 12B12M_C) compared with the two vaccinations given alone at 12 or 13 months -rMenB+OMV NZ alone (32%-44% all and 16%-25% at least possibly related AEs in groups 12B13M, 12B13M_C) or Priorix-Tetra alone (36% all and 14% at least possibly related AEs in group 12M13B15B). All 6 febrile seizures reported after vaccination with rMenB+OMV NZ occurred anywhere from 9 to 45 days after vaccination and were therefore beyond the 2-day duration of fever associated with rMenB+OMV NZ vaccination.

No deaths were reported in this study. A total of 113 subjects experienced SAEs with two subjects in group 12B12M (one subject had febrile convulsions 9 days after concomitant vaccination with rMenB+OMV NZ and Priorix-Tetra and one subject with pyrexia 2 days after concomitant vaccination with rMenB+OMV NZ and Priorix-Tetra) having SAEs that were judged to be possibly related to the study vaccination.

V72P13E2 is an extension study of V72P13E1. The interim report for V72P13E2 submitted with this application contains safety data collected for 30 days following a booster (third) dose of rMenB+OMV NZ administered at one year after two catch-up doses of rMenB+OMV NZ, previously administered to toddlers at either 12 and 14 or 13 and 15 months of age in study V72P13E1 (Groups 2a and 2b). Out of 508 enrolled subjects, 85 subjects from these two-dose schedule groups were analysed for safety. The majority of the subjects (89%-99%) experienced solicited local and systemic reactions within 7 days after vaccination with rMenB+OMV NZ; most of the reactions were mild to moderate in severity. Most of the local and systemic reactions occurred within the first three days of vaccination. These reactions were transient with few continuing past the day 7 observation window. The majority of reactions were mild or moderate in nature. The most common local reaction was tenderness, reported in 94% of subjects, with 18% of the subjects having severe tenderness (crying when the injected limb was moved). A total of 70%-76% subjects had erythema, with 3% of subjects in group 2b having severe erythema (>100mm). Other local reactions reported were induration and swelling. The percentages were similar between the vaccination groups.

The most common systemic reaction was irritability, reported in 60%-82%, with 1%-6% of the subjects having severe irritability. Other systemic reactions reported were change in eating habits, sleepiness, vomiting, diarrhoea, unusual crying, rash and fever. Fever (≥38°C) was reported in 33% of subjects in both groups, with none of the subjects reporting temperature ≥40°C. Antipyretic medications were administered as treatment to 30%-35% of the subjects and none of the subjects had medically attended fever. Percentages of subjects with AEs following the booster dose were 33%-49% with 22%-28% being at least possibly related to the study vaccination. There were no SAEs or deaths reported during the study.

The most common AE by preferred term was “injection site induration” which was reported in, 17%-24% of subjects. Most of the other AEs by preferred term were due to the local injection site reactions and some of the systemic reactions continuing past 7-days after the vaccination.

V72P6 was a phase 2, open label, multi-centre, controlled, randomized study conducted in the UK in healthy infants 2 months of age at time of enrolment. The main aim of the study was to explore the safety and immunogenicity of the rMenB vaccine with or without OMV NZ when administered to healthy infants at 2, 4 and 6 months of age, followed by a fourth dose at 12 months of age concomitantly with infant routine vaccinations. A total of 147 children were enrolled and included in the safety population, and 73 were vaccinated with rMenB+OMV NZ (50 received at least one dose as part of the primary series, 23 subjects received a single dose at 12 months of age). Most reactions occurred within the first three days and few were ongoing on day 7. All solicited reactions were transient with few continuing past the day 7 observation window. The majority were mild or moderate in nature.

Erythema was the most common solicited local reaction across vaccine groups to the study vaccines and the concomitant vaccinations. Irritability was the most common solicited systemic reaction followed by sleepiness across all groups after any vaccination. Most systemic reactions occurred within the first three days and few were ongoing on day 7. Urticarial rash was reported by three subjects in the rMenB+OMV NZ group. Fever >38.5°C was observed more commonly in the groups receiving rMenB+OMV NZ (in 6 subjects) as compared to the groups not receiving this vaccine (3 subjects) across the injections. More subjects in the rMenB+OMV NZ group (69%) were administered antipyretics or analgesics than in the other vaccine groups (35%). Other AEs, irrespective of relatedness to study vaccines were reported by 88% to 96% of subjects across the vaccine groups. A total of 20 SAEs in 18 subjects were reported during the course of the study, including 10 SAEs in the rMenB+OMV NZ group; none of these was considered to be possibly related to the study vaccine.

No deaths or discontinuations due to the study vaccines occurred. The rMenB+OMV NZ vaccine was well-tolerated in combination with routine vaccinations in healthy infants, although it was more reactogenic than the rMenB vaccine without OMV NZ.

V72P9: A total of 60 infants were enrolled and included in the safety set; 30 were vaccinated with rMenB+OMV NZ. Percentages of subjects reporting at least one solicited local reaction were slightly lower in the rMenB group (range, 83% to 90%) compared with the rMenB+OMV NZ group (range, 93% to 96%). The most common solicited local reactions were erythema (range, 73% to 87%: rMenB and 87% to 96%: rMenB+OMV NZ) and induration (range, 40% to 50%: rMenB and 57% to 67%: rMenB+OMV NZ). The most common solicited systemic reactions were irritability (range, 33% to 47% in the rMenB group and 47% to 67% in the rMenB+OMV NZ group), sleepiness (23% in the rMenB group and 15% to 37% in the rMenB+OMV group), and change in eating habits (3% to 27%: rMenB and 19% to 28%: rMenB+OMV NZ. Other indicators of reactogenicity (i.e. use of analgesics/antipyretics) were reported by lower percentages in the rMenB group than rMenB+OMV NZ group after each injection (67% and 90% respectively). Fever (≥38°C) was reported by a similar and low percentage of subjects in both vaccine groups (23% in the rMenB group and 20% in the rMenB+OMV NZ group. As expected with the addition of OMV NZ, mild fever was experienced generally within 6 hours of injection and mostly resolved within one day, but the frequency decreased after the third injection. One subject, a recipient of the rMenB+OMV NZ vaccine, reported fever of 40.4°C and had a convulsion on study day 199, on day 5 after the third injection. The subject was hospitalized and the fever resolved the same day after treatment with ibuprofen and paracetamol. The fever had been preceded by cough on day 4 and was concurrent with otitis media and tonsillitis. This occurrence of fever was also accompanied by sleepiness, vomiting, diarrhoea, unusual crying and irritability. All the events (febrile convulsion, cough, otitis media and tonsillitis) were considered to be unrelated to study vaccine.

Overall, lower percentages of unsolicited AEs were reported in the rMenB+OMV NZ group (77%) as compared with the rMenB group (83%). A total of 6 SAEs were reported during the course of the study, with 1SAE (in subject 01/001 discussed above) in the rMenB+OMV NZ group. None of the SAEs was assessed as related to the study vaccines.

No deaths or withdrawals due to AEs were reported during the study period.

V72P12: A total of 1885 infants were enrolled, 1882 were included in the safety set, and 1570 were vaccinated with rMenB+OMV NZ. Most local and systemic reactions occurred within the first three days. All these local and systemic reactions were transient with few continuing past the day 7 observation window. The majority of reactions were mild or moderate in nature. Overall, the local reactions after each rMenB+OMV NZ vaccination were similar across the vaccination groups with the most commonly reported local reaction being erythema (62% to 69% in Group B+R246 and 65% to 70% in Group B+R234) after each vaccination. The percentage of subjects reporting local reactions, as well as the severity of the reactions did not consistently increase with subsequent doses. The most common systemic reaction reported was irritability (71% to 74% in Group 1 [B+R246] and 66% to 79% in Group 3 [B+R234]) after each vaccination. The percentages for systemic reactions were lower in the routine only vaccination group when compared with the rMenB+OMV NZ vaccination groups. Higher percentages were reported after concomitant vaccinations compared with the rMenB+OMV NZ vaccination given separately from the routine vaccines. Fever (i.e., body temperature ≥38.0°C) after each vaccination was reported for 44% to 62% of subjects after receiving rMenB+OMV NZ concomitantly with routine vaccinations (2, 4, 6-month and 2, 3, 4-month schedules), compared with 23% to 36% after routine vaccination only (2, 3, 4-month schedule) and 25% to 41% after rMenB+OMV NZ vaccination given separately (2, 4, 6-month schedule) from routine vaccinations. After the first vaccination, ≤3% of the subjects receiving rMenB+OMV NZ were reported with body temperatures of 39.5°C or above, compared with ≤1% in the Routine group. After the second and third vaccinations, percentages were low and similar in all groups except for Group 1(B+R246) in which ≤4% subjects had temperature of 39.5°C or above. Overall, ≤7% of subjects receiving rMenB+OMV NZ were reported with temperatures of 39.5°C or above after any vaccination, compared with 2% in the routine vaccine group.

Overall, the most commonly reported AEs after any vaccination were injection site induration (many considered at least possibly related to vaccination) and pyrexia, nasopharyngitis, cough, rhinitis, bronchitis, upper respiratory tract infections which were mostly considered unrelated to vaccination.

Overall rates of Serious Adverse Events were low and similar among groups after each vaccination with 0-1% of the SAEs being at least possibly related to the study vaccination. Most SAEs were reported after the third vaccination. A total of 10 subjects experienced febrile or non-febrile seizures following study vaccinations: 8 were reported as serious, 4 were febrile seizures and 4 were judged to be at least possibly related seizures. One febrile seizure was temporally related to study vaccination as it occurred 2 days after the second dose of rMenB+OMV NZ given separately. Four non-febrile seizures occurred within one day of study vaccination: two following vaccination with routine vaccines and two following vaccination with rMenB+OMV NZ, either given alone or with routine vaccines.

There were two cases of Kawasaki disease that were reported during the time period of this study. These cases are discussed below.

No deaths were reported in this study.

8.4.1.2.2. Adolescents and adults

V72P4: A total of 54 adults were enrolled, 53 were in the safety set, and 53 were vaccinated with rMenB+OMV NZ in the study (one subject was withdrawn from the study on enrolment day). After any rMenB+OMV NZ vaccination, almost all of the subjects (98%-100%) experienced reactogenicity, mainly due to local reactions. Most local and systemic reactions occurred within the first three days and most were transient with few continuing past the day 7 observation window. The majority of the reactions and most were mild or moderate in severity. The most common local reaction after rMenB+OMV NZ vaccination was injection site pain (96-100%) with 13% to 18% subjects reporting severe pain. The most common systemic reaction reported

after the first vaccination was malaise (30%), after the second vaccination was myalgia (37%), and after the third vaccination was malaise (52%). The percentage of subjects reporting malaise, myalgia, arthralgia, and headache increased with subsequent vaccinations. After the first vaccination and second vaccinations, 0 to 6% subjects reported severe systemic reactions, the highest being severe malaise and myalgia. After the third vaccination, 0 to 14% reported severe systemic reactions, the highest being severe myalgia. Two subjects reported temperature 38°C to <39°C after the first vaccination and one subject reported a temperature of 39.6°C after the second vaccination. None of the subjects reported temperature ≥ 40°C. A total of 24 out of 53 (45%) subjects experienced at least one other (unsolicited) AE and a total of 7 out of 53 (13%) subjects had at least possibly related. The most commonly reported AEs after any vaccination were injection site pain and nasopharyngitis (11% each) followed by rhinitis (6%), bronchitis (4%), gastritis (4%) and injection site induration (4%). The most common AE that was possibly or probably related after any vaccination was injection site pain (9%), followed by injection site induration (4%), chills (2%) and (other) pain (2%). Two subjects were withdrawn from the study due to AEs judged as unrelated to study vaccination (one pharyngitis, one pregnancy).

No deaths or SAEs were reported during this study.

V72P5: A total of 70 adults were enrolled and included in the safety population; 28 subjects were vaccinated with rMenB+OMV NZ. Overall, the reactogenicity profiles were similar for the rMenB+OMV NZ and rMenB+OMV NW vaccines, whereas the rMenB vaccine appeared to be less reactogenic. Most local and systemic reactions were either mild or moderate. At least one local reaction was reported within 7 days postvaccination by all subjects (100%) in the rMenB + OMV NZ group and in the rMenB + OMV NW and by all but one subject (93%) in the rMenB group. In both the rMenB + OMV NZ group and in the rMenB + OMV NW group; all but one subject (96%) reported at least one systemic reaction within 7 days postvaccination. In the rMenB group, 79% of the subjects reported at least one systemic reaction within 7 days postvaccination. Pain at the injection site was the most commonly reported solicited local reaction, reported by all subjects (100%, and severe in 32%). Other indicators of reactions (use of analgesics/antipyretics and stayed home due to a reaction) were reported by 46% of the subjects in the rMenB + OMV NZ and rMenB + OMV NW groups, while no subject reported such reactions in the rMenB group. Severe pain had an onset within 6 hours and resolved within the first 2 days. Induration was experienced by 68% of subjects, and erythema by 39%. Myalgia was the most common systemic reaction, reported by 82% of subjects: severe myalgia was reported by 25%. Headache, the next most commonly reported systemic reaction, was experienced by 57%. Systemic reactions were most frequently reported at 6 hours on day 1 and on day 2, and then rapidly declined. The frequency of local and systemic reactions and other indicators of reactogenicity were similar after the first, second, and third vaccine dose. At least one unsolicited AE was reported by 21% of subjects. One subject in the rMenB+OMV NZ group had an SAE, (HIV infection assessed as unrelated to vaccination. Two abnormal laboratory values in subjects receiving rMenB+OMV NZ were assessed as clinically significant; these were one case of elevated γGT value (131 U/L), and one positive HIV test (described above). No abnormal laboratory value was assessed as related to the study vaccine. No unexpected or otherwise clinically significant AEs related to the vaccines administered were reported in this study.

No deaths occurred during the study.

8.4.1.3. Pooled analysis

8.4.1.3.1. Unsolicited AEs: Infants and toddlers

Total number of AEs

- **Infants and toddlers**

Unsolicited AE data for infants following a 2, 4 and 6-month schedule of rMenB+OMV NZ administered concomitantly with routine vaccines were integrated from studies V72P6,

V72P12, and V72P13. A total of 3155 subjects received at least one dose of rMenB+OMV NZ with concomitant routine vaccines in these 3 studies in a 2, 4 and 6-month schedule. Between study day 1 and 7 months of age (1 month after the third dose), the percentage of subjects experiencing unsolicited AEs in the rMenB+OMV NZ with concomitant routine vaccines, MenC with concomitant routine vaccines and, routine only groups were 77%, 63% and 71%, respectively, with 52%, 42% and 34% considered by the investigator to be at least possibly related to vaccination. SAEs were infrequent, occurring in 4%, 3% and 3% of subjects in the rMenB+OMV NZ with concomitant routine vaccines, MenC with concomitant routine vaccines, and routine only groups, respectively from study V72P6, V72P12, and V72P13; Between 7 and 12 months of age (i.e., 1 month after third vaccination to study termination), the percentage of subjects experiencing unsolicited AEs in the rMenB+OMV NZ with concomitant routine vaccines, MenC with concomitant routine vaccines, and routine only groups were 54%, 35% and 56%, respectively. Less than 1% of subjects experienced AEs that were possibly or probably related to the study vaccines in all three groups. SAEs were infrequent, occurring in 5%, 3% and 5% of subjects in the rMenB+OMV NZ with concomitant routine vaccines, MenC with concomitant routine vaccines, and routine only groups, respectively. Between study day 1 and 5 months of age in the group receiving rMenB+OMV NZ with concomitant routine vaccines in the 2, 3 and 4-month schedule, the unsolicited AE rate was 66%, lower than that in the group receiving the same vaccines in the 2, 4 and 6-month schedule (77%). This could be explained by the shorter reporting period in the analysis (5 months vs. 7 months) due to the shorter vaccination schedule. More subjects (85%) in the group receiving rMenB+OMV NZ alone at 2, 4 and 6 months of age (routine vaccines at 3, 5 and 7 months of age) experienced unsolicited AEs during the 6 month reporting period. Between 1 month after the infant series (i.e., approximately 5 to 7 months of age) and 12 months of age, the rates for any AEs (51% to 55%) and SAEs (3% to 5%) were similar regardless of vaccine schedules. Possibly or probably related AEs were infrequent during this study period (1% or less). This pattern likely reflects the background AE rates in infants.

In summary, 4100 infants received at least one dose of the rMenB+OMV NZ vaccine in various schedules. Within 30 days after the first, second, and third doses, 37%, 44%, and 47% of subjects experienced any AEs, respectively; and 27%, 31%, and 31% experienced AEs that were possibly or probably related to the study vaccine. SAEs were infrequent, occurring in approximately 1%.

- **Vaccine naive older infants and toddlers (2-dose schedule)**

In the 30 subjects who received a 2-dose primary series of rMenB+OMV NZ vaccine at 6 to 8 months of age at enrolment in V72P9 study, 50% of subjects experienced AEs after the first and second dose of the vaccine. Rates of possibly or probably related AEs were 23% and 29% after the first and second doses, respectively. No SAEs were observed after the first two doses of vaccines. The percentage of subjects who experienced unsolicited AEs after a two-dose primary schedule of rMenB+OMV NZ in vaccine naive toddlers in V72P13E1 study was 17% after the first dose and 15% after the second dose of the vaccine, 3% had AEs considered by the investigator to be at least possibly related to vaccination and <1% to 6% were considered.

- **Booster dose in toddlers (at 12 months of age)**

The percentage of subjects who experienced unsolicited AEs after the booster dose in subjects who received a 3-dose infant primary series was 44% and 74% for subjects who received rMenB+OMV NZ alone and those who received rMenB+OMV NZ with concomitant Priorix-Tetra vaccine, respectively.

In V72P9 study, of 27 toddlers (12 months of age) who received the third (booster) dose of the rMenB+OMV NZ vaccine, 56% experienced any AEs and 22% possibly or probably related AEs. One SAE occurred 4 days after the vaccination.

- **Booster dose in toddlers (at 26 or 27 months of age)**

In the two-dose schedules in V72P13E2, the percentages of subjects with unsolicited AEs following the booster dose were 33%-49% with 22%-28% (higher in B13_15_27) being at least possibly related to the study vaccination. There were no SAEs or deaths reported during the study.

Unsolicited AEs: Details of AEs

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 swelling 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). For other vaccination schedules, between study day 1 and 1 month after the infant series, (approximately 5 to 7 months of age), injection site induration, injection site swelling and injection site erythema were also most frequently reported in subjects receiving rMenB+OMV NZ with concomitant routine vaccines at the 2, 3 and 4-month schedule (range, 11% to 32%) and subjects receiving rMenB+OMV NZ alone at 2, 4 and 6 months of age (routine vaccines at 3, 5 and 7 months of age; range, 8% to 34%), but in the latter group were reported less frequently than in those receiving rMenB+OMV NZ with concomitant routine vaccines at the 2, 4 and 6-month. This trend reflected what was observed for solicited AEs. Upper respiratory tract infections, rhinitis, cough, otitis media and bronchitis were among the most frequently reported non-injection site related AEs; the event rates were in general similar between the vaccine groups. Between 1 month after the infant series and 12 months of age, injection site AEs were not reported; rhinitis, otitis media, bronchitis, and upper respiratory tract infections, were among the most frequent AEs reported. The event rates were similar between the vaccine groups, likely reflecting the background incidence rates of these commonly occurring medical conditions in infants. Within 30 days after the first, second and third dose of rMenB+OMV NZ in any dose schedules, injection site induration, erythema and swelling were the most frequently reported AEs. Upper respiratory tract infection, pyrexia, rhinitis, and otitis media were the most frequent non-injection site AEs. Slightly more AEs were observed with subsequent doses, but it is likely the confounding effect of the increasing age of the subjects.

- **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 at enrolment in study V72P9, 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 naïve 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. Most of the other AEs by preferred term were due to the local injection site reactions and systemic reactions that were originally solicited but continued past 7-days after vaccination. Almost all of the injection site reactions were at least possibly related to the study vaccination.

- **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. Most of the other AEs by preferred term were due to the local injection site reactions and systemic reactions that were originally solicited but continued past 7-day after the vaccination. Almost all of the injection site reactions were considered at least possibly

related to the study vaccination. The most frequently experienced unsolicited AEs in older, vaccine naïve 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.

- **Booster dose in toddlers (at 26 or 27 months of age)**

The most common AE by preferred term was "injection site induration" which was reported in, 17%-24% in the two-dose schedules (groups B13_15_27 and B12_14_26) in V72P13E2. Most of the other AEs by preferred term were due to the local injection site reactions and some of the systemic reactions continuing past 7-days after the vaccination. Almost all of the injection site reactions were at least possibly related to the study vaccination.

8.4.1.3.2. Unsolicited AEs: Adolescents and adults

Total numbers of AEs

- **11 to 17 years of age**

A total of 1631 adolescent subjects who received at least one dose of rMenB+OMV NZ (1503) or placebo (128) vaccine were included in the analysis of unsolicited AEs. The data of unsolicited AEs are presented up to study month 4 (visit 4) of the study. From study day 1 to 30 days after the third vaccination (visit 4), similar frequency of unsolicited AEs was reported by subjects receiving one, two or three doses of rMenB+OMV NZ or placebo (39%-46%). Approximately 13% to 18% of these AEs in the rMenB+OMV NZ vaccine groups were assessed by the investigator to be at least possibly or probably related to the study vaccination (overall, 13% to 18% of the subjects across vaccine groups). Lower percentages of subjects reported possibly or probably related AEs in the placebo group (12%). SAEs were infrequently reported by no more than four subjects across vaccine groups. None of these were assessed to be related to the study vaccination. Overall, one subject withdrew from the study due to an AE (convulsion with onset on study day 1 with less than 1 day of duration); the AE was assessed to be unrelated to the study vaccination. During the 30 days following each dose, both "any" and possibly or probably related AEs decreased with subsequent vaccinations in both the rMenB+OMV NZ and placebo groups. The percentages of rMenB+OMV NZ recipients reporting any AEs were similar to those observed in the placebo group across the three doses. About 3% to 10% of these AEs were assessed to be possibly or probably related to the study vaccination. There was a trend for possibly or probably related AEs to be reported by a slightly higher number of subjects in the rMenB+OMV NZ group compared with subjects in the placebo group (range, 7% to 10% vs. 3% to 6%).

- **18 to 50 years of age**

The unsolicited AE rates observed in the adult subjects up to 3 months after the first dose were lower than those in the adolescent subjects with the same dose schedule of rMenB+OMV NZ (0-1-month schedule: 18% vs. 43%; 0-2-month schedule: 32% vs. 46%). Reporting rates for any and possibly or probably related AEs were lower in the adult subjects than the adolescent subjects with similar dose schedule up to month 3 of the studies. SAEs were not reported by any adult subjects. No deaths were reported in this study.

Unsolicited AEs: Details of AEs

- **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%) and was similarly reported across the different dose schedules groups 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, injections 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. In the group that received three doses of the rMenB+OMV NZ vaccine, the percentage of subjects reporting AEs after each vaccination was similar to the groups receiving two doses. AEs assessed as possibly or probably related to the study vaccine were reported by no more than 10% of subjects across dose groups with slightly lower frequency in the placebo group. 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. As seen previously, the percentage of subjects who reported AEs decreased after second and third vaccine doses. Following the fourth dose at month 6, the most commonly reported unsolicited AE was nasopharyngitis (range, 1% to 4) and was similarly reported across the different dose groups. AEs assessed as possibly or probably related to the study vaccine were reported by no more than 11% of subjects across dose groups: The most common AE that was possibly or probably related after any vaccination was injection site pain (range, 0-4%).

· **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 induration 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-day observational period: swelling and injection site pain and injection site induration. Only one severe AE (injections site pain) was reported during the 7-day observational period by one adult subject (02/032) in study V72P4 after the first dose of rMenB+OMV NZ.

8.4.2. Treatment-related adverse events (adverse drug reactions)

8.4.2.1. Pivotal studies

8.4.2.1.1. V72P10

· **Local reactions**

Within the 7-day observation window after the first vaccination, more than half of the subjects who received rMenB+OMV NZ reported erythema, the majority of which were of mild intensity. About 40% of the subjects reported swelling and induration, with most of the cases being mild. Pain was reported by a large proportion of subjects and most of them reported pain at moderate intensity. Severe local reactions after first vaccination were infrequent and were mostly reported as severe pain. All the local reactions were reported by a lower percentage of subjects in the placebo group except pain; there was no substantial difference between the rMenB groups and the placebo groups in the frequency of subjects reporting pain. In the groups that received two doses of the vaccine, the group that received the second dose with an interval of two months (rMenB02) showed better tolerability in terms of percentage of subjects reporting erythema, swelling and induration after the second vaccination, than the group that received the second dose with an interval of one month (Table 52). However there was no difference

between these two schedules in the percentage of subjects reporting pain. In the group that received three doses of the vaccine, the reactogenicity profile after the third vaccination was similar to the reactogenicity after the second vaccination in the group that received two doses, two months apart. Overall, the placebo group showed lower percentage of subjects reporting erythema, induration and swelling; pain was reported by a substantial percentage of subjects. A large proportion of these reactions were mild to moderate in intensity and severe reactions were mostly reported as severe pain.

Table 52: Number (%) of Subjects Aged 11 to 17 Years with Local Reactions, After Each Vaccination Days 1 to 7- Safety population

		rMenB0	rMenB01	rMenB02	rMenB012	Placebo
		N=375	N=375	N=380	N=373	N=128
First Vaccination	Erythema	197(53%)	196(52%)	211(56%)	209(56%)	51(40%)
	>100mm	0	2(1%)	0	0	0
	Swelling	157(42%)	145(39%)	128(34%)	155(42%)	25(20%)
	>100mm	1(<1%)	1(<1%)	3(1%)	0	0
	Induration	146(39%)	157(42%)	137(36%)	163(44%)	34(27%)
	>100mm	0	2(1%)	0	0	0
	Pain	347(93%)	347(93%)	341(90%)	331(89%)	110(86%)
	Severe	64(17%)	57(15%)	73(19%)	62(17%)	11(9%)
		N=351	N=356	N=347	N=342	N=124
Second Vaccination	Erythema	120 (34%)	185 (52%)	128 (37%)	182 (53%)	38 (31%)
	>100mm	0	1/356(<1%)	0	1/342(<1%)	0
	Swelling	63 (18%)	141 (40%)	60 (17%)	135 (39%)	19 (15%)
	>100mm	1 (<1%)	2 (1%)	0	3 (1%)	0
	Induration	75 (21%)	139 (39%)	70(20%)	154 (45%)	29 (23%)
	>100mm	0	0	0	2(1%)	0
	Pain	205 (58%)	306 (86%)	226 (65%)	297 (87%)	88 (71%)
	Severe	11 (3%)	49 (14%)	7 (2%)	44 (13%)	11 (9%)
		N=343	N=350	N=341	N=332	N=121
Third Vaccination	Erythema	107 (31%)	109 (31%)	168 (49%)	158 (48%)	35 (29%)
	>100mm	1 (<1%)	0	1 (<1%)	1 (<1%)	0
	Swelling	59 (17%)	77 (22%)	119 (35%)	129 (39%)	14 (12%)
	>100mm	0	0	1 (<1%)	1 (<1%)	0
	Induration	75 (22%)	76 (22%)	122 (36%)	135 (41%)	14 (12%)
	>100mm	0	0	1 (<1%)	0	0
	Pain	197 (57%)	170 (49%)	285 (84%)	261 (79%)	82 (68%)
	Severe	7 (2%)	6 (2%)	58 (17%)	42 (13%)	6 (5%)

- **Systemic reactions and other indicators**

After receiving one dose of rMenB+OMV NZ, about half of the subjects reported malaise, myalgia and headache. Arthralgia and nausea were reported by relatively lower percentage of subjects (Table 53). A similar trend was also observed in the placebo. There was no clear and consistent difference among the vaccine groups, in the percentage of subjects reporting each of the systemic reactions after receiving each vaccination. Most of the subjects reported mild to moderate systemic reactions and severe reactions were reported at lower frequency. A large proportion of these reactions were reported during three days following each vaccination and resolved within the 7-day observation window.

Table 53: Number (%) of Subjects Aged 11 to 17 Years with Systemic Reactions, After Each Vaccination Days 1 to 7- Safety Set

		rMenB0	rMenB01	rMenB02	rMenB012	Placebo
		N=375	N=375	N=380	N=373	N=128
First Vaccination	Malaise	216(58%)	206(55%)	210(55%)	204(55%)	62(48%)
	Severe	33(9%)	22(6%)	25(7%)	24(6%)	4(3%)
	Myalgia	164(44%)	178(47%)	176(46%)	164(44%)	53(41%)
	Severe	27(7%)	22(6%)	22(6%)	27(7%)	5(4%)
	Arthralgia	88(23%)	88(23%)	86(23%)	101(27%)	24(19%)
	Severe	5(1%)	5(1%)	9(2%)	10(3%)	0
	Headache	157(42%)	188(50%)	176(46%)	170(46%)	47(37%)
	Severe	22(6%)	15(4%)	20(5%)	14(4%)	2(2%)
	Nausea	64(17%)	72(19%)	67(18%)	76(20%)	22(17%)
	Severe	5(1%)	4(1%)	4(1%)	8(2%)	2(2%)
		N=351	N=356	N=347	N=342	N=124
Second Vaccination	Malaise	103 (29%)	174 (49%)	115 (33%)	183 (54%)	44 (35%)
	Severe	6 (2%)	23 (6%)	7 (2%)	26 (8%)	3 (2%)
	Myalgia	76 (22%)	138 (39%)	91((26%)	139 (41%)	49 (40%)
	Severe	6 (2%)	23 (6%)	4 (1%)	22 (6%)	4 (3%)
	Arthralgia	37 (11%)	74 (21%)	56 (16%)	76 (22%)	20 (16%)
	Severe	3 (1%)	14 (4%)	3 (1%)	12 (4%)	1 (1%)
	Headache	102 (29%)	152 (43%)	112/347(32%)	155 (45%)	41 (33%)
	Severe	11/351(3%)	17 (5%)	13 (4%)	22 (6%)	4 (3%)
	Nausea	42 (12%)	54 (15%)	46 (13%)	63(18%)	18 (15%)
	Severe	3 (1%)	3 (1%)	4 (1%)	8 (2%)	1 (1%)
		N=343	N=350	N=341	N=332	N=121
Third Vaccination	Malaise	103 (30%)	77 (22%)	160 (47%)	147 (44%)	35 (29%)
	Severe	4 (1%)	5 (1%)	25 (7%)	18 (5%)	1 (1%)
	Myalgia	63 (18%)	65 (19%)	141 (41%)	120 (36%)	34 (28%)
	Severe	6 (2%)	3 (1%)	18 (5%)	20 (6%)	1 (1%)
	Arthralgia	33 (10%)	30 (9%)	72 (21%)	69 (21%)	15 (12%)
	Severe	0	0	9 (3%)	10 (3%)	0
Headache		72 (21%)	86 (25%)	126 (37%)	140 (42%)	34 (28%)
Severe		6 (2%)	6 (2%)	17 (5%)	18 (5%)	4 (3%)
Nausea		35 (10%)	34 (10%)	49 (14%)	59 (18%)	19 (16%)
Severe		2 (1%)	2 (1%)	5 (1%)	6 (2%)	1 (1%)

Overall, not more than 5% of the subjects across the vaccine groups reported fever (≥38°C) and there was no difference between the groups that received rMenB and placebo in terms of percentage of subjects reporting fever. Medically attended fever was reported by ≤1% subjects across the vaccine groups. None of the subjects reported a body temperature of >40°C (Table 54).

A higher percentage of subjects in the rMenB vaccine groups stayed home and/or had taken analgesics than in the placebo group. No clear and consistent difference was noted among the rMenB vaccine groups in the percentage of subjects reporting the 'other indicators of reactogenicity'.

Table 54: Number (%) of Subjects Aged 11 to 17 Years with Other Indicators of Reactogenicity, After Each Vaccination Days 1 to 7- Safety Set

		rMenB0	rMenB01	rMenB02	rMenB012	Placebo
		N=375	N=375	N=380	N=373	N=128
First Vaccination	Fever (≥ 38C)	9 (2%)	9 (2%)	14 (4%)	12 (3%)	5 (4%)
	≥ 41 C	0	0	0	0	0
	Med. Att. Fever	1/281 (<1%)	1/266 (<1%)	0	0	1/108 (1%)
	Stay Home	59/350 (17%)	47/352 (13%)	56/348 (16%)	55/342 (16%)	7/122 (6%)
	Analge. Med.Used	135 (36%)	133 (35%)	129 (34%)	134 (36%)	26 (20%)
	Antipyr. Med.Used	6/158 (4%)	5/157 (3%)	10/162 (6%)	4/162 (2%)	3/54 (6%)
Second Vaccination	Fever (≥ 38C)	5/351 (1%)	17/356 (5%)	8/347 (2%)	11/342 (3%)	2/124 (2%)
	≥ 41 C	0	0	0	0	0
	Med. Att. Fever	0	0	2/304 (1%)	1/257(<1%)	0
	Stay Home	14/327 (4%)	33/336 (10%)	23/331 (7%)	39/323(12%)	4/120(3%)
	Analge. Med.Used	65/351(19%)	83/356(23%)	56/347(16%)	109/342 (32%)	18/124(15%)
	Antipyr. Med.Used	3/154(2%)	5/153(3%)	6/153(4%)	9/148(6%)	1/52(2%)
Third Vaccination	Fever (≥ 38C)	6/343(2%)	4 /350(1%)	13/341(4%)	18/331(5%)	4/121(3%)
	≥ 41 C	0	0	0	0	0
	Med. Att. Fever	0	0	0	0	0
	Stay Home	15/313(5%)	10/323(3%)	34/320(11%)	29/309(9%)	2/112(2%)
	Analge. Med.Used	42/343(12%)	52/350(15%)	85/341(25%)	90/332(27%)	17/121(14%)
	Antipyr. Med.Used	1/149(1%)	1/153(1%)	7/153(5%)	6/146(4%)	0

8.4.2.2. Other studies

8.4.2.2.1. Infants and toddlers

Studies V72P12 and V72P13 provide data to support the administration of three doses of rMenB+OMV NZ vaccine, given one or two months apart, as the primary vaccination series in infants starting at 2 months of age. Almost all subjects (range, 97% to 99%) experienced local or systemic reactions after each vaccination with rMenB+OMV NZ at 2, 4, and 6 months of age concomitantly with routine infant vaccines as seen in the total rMenB+OMV NZ group (group MenB total). The frequency of subjects who reported any reactions did not increase following subsequent vaccinations. Solicited local and systemic AEs for the rMenB+OMV NZ groups were similar: percentages for the routine vaccines only and the MenC vaccine administered concomitantly with routine groups were comparable with each other, and were lower than for rMenB+OMV NZ total group. Similarly, the incidence of any other reactions followed a similar trend among the three groups (rMenB+OMV NZ: range, 71% to 81%; Routine: range, 43% to 52%; MenC: range, 36% to 52%). After each of the three vaccinations, the percentages of subjects experiencing solicited local or systemic reactions were similar for subjects receiving rMenB+OMV NZ vaccination concomitantly with routine vaccines at either the 2, 4 and 6 months of age schedule or at the 2, 3 and 4 months of age schedule. However, when rMenB+OMV NZ was administered at 2, 4, 6 months of age without concomitant routine vaccines (given at 3, 5, 7 months) the reactogenicity of the vaccine was incrementally improved. Subjects receiving rMenB+OMV NZ alone at 2, 4 and 6 months of age exhibited slightly lower rates of local and systemic reactions compared with subjects receiving rMenB+OMV NZ with routine vaccines alone. Again, the percentages of subjects who experienced reactions did not increase with subsequent vaccinations in all vaccine groups. Lower rates were observed for subjects who

received routine vaccines alone at either 3, 5, and 7 months of age or at 2, 3 and 4 months of age then for subjects receiving the rMenB+OMV NZ vaccine concomitantly with the routine vaccine.

· **Vaccine naive older infants and toddlers (2-dose schedule)**

The safety and tolerability of a two-dose schedule for rMenB+OMV NZ administered to infants starting at 6 to 8 months of age at enrolment and toddlers starting at 12 or 13 months of age at enrolment were investigated in studies V72P9 and V72P13E1, respectively. After the first and second injections of rMenB+OMV NZ at 6 and 8 months of age, the percentages of subjects reporting at least one solicited local, systemic or other indicators of reactogenicity were 96% to 100%. A similar reactogenicity profile was observed when rMenB+OMV NZ vaccine was given as a two-dose schedule to vaccine naive toddlers at 13 and 15 or 12 and 14 months (range, 95%-97%).

· **Booster dose in toddlers (at 12 months of age)**

Percentages of subjects with any solicited reactions were similar between subjects who received a 12-month booster administered with or without concomitant Priorix-Tetra, vaccination, in subjects who had previously received three doses of rMenB+OMV NZ at 2, 4, and 6 months of age in the parent study V72P13 (95% to 97). A similar reactogenicity profile was observed for the booster dose administered at 12 months of age to subjects who had previously received a two-dose primary course of rMenB+OMV NZ vaccinations at approximately 6 and 8 months of age in study V72P9 (100%). The incidence of any solicited local, systemic, or other indicators of reactogenicity (analgesic and antipyretic used) was generally similar for third or fourth dose boosters of rMenB+OMV NZ administered at 12 months of age.

· **Booster dose (at 26 or 27 months of age)**

Most subjects (89%-99%) in the V72P13E2 groups who had received 2 toddler doses in study V72P13E1 experienced solicited local or systemic reactions within 7 days after booster vaccination with rMenB+OMV NZ; most of the reactions were mild to moderate in severity, and transient.

8.4.2.2.2. Adolescents and adults

· **11 to 17 Years of age**

A majority of subjects reported local or systemic reactions within 7 days after each vaccination in the rMenB+OMV NZ groups as well as in the placebo groups. Within the 7-day observation window after each vaccination, the solicited AEs were reported by a higher percentage of subjects in the rMenB+OMV NZ groups than in the placebo group. The overall reactogenicity profile was similar across the 1, 2 and 3 dose schedules of rMenB+OMV NZ vaccine. Of particular note, the solicited AEs profile of the 2-dose schedule, administered with an interval of 1 or 2 months, as well as the 3-dose schedule were comparable. The percentage of rMenB+OMV NZ recipients reporting any solicited AEs ranged from 87% to 94% by dose compared to 78% to 92% for placebo subjects after the first dose (Table 55). A trend towards decreased reports of solicited AEs with subsequent vaccinations was also observed in both the rMenB+OMV NZ and placebo groups. In the 7 days following vaccinations at 6 months, solicited AEs were reported at similar rates to those reported after the vaccinations of the primary course. After the booster vaccination was administered, the frequency of solicited local and systemic reactions was higher in the vaccine groups that received rMenB+OMV NZ than the groups that received placebo at this visit. In the groups with two or three doses of rMenB+OMV NZ vaccine in the primary vaccination course, there was an indication of increase in tolerability to the vaccine administered as there was a slight reduction in the frequency of these reports upon subsequent injections in the primary vaccination course.

Table 55: Overview of Solicited Adverse Events of rMenB+OMV NZ Vaccine, by Vaccination in Subjects 11 to 17 Years of Age

Number (%) of Subjects With Solicited AEs						
	Dose 1		Dose 2		Dose 3	
	rMenB+ OMV NZ[a] N=1503	Placebo[b] N=128	rMenB+ OMV NZ[c] N=1039	Placebo[d] N=124	rMenB+ OMV NZ[e] N=332	Placebo[f] N=121
Any	1410 (94%)	118 (92%)	938 (90%)	104 (84%)	289 (87%)	94 (78%)
Local	1390 (92%)	114 (89%)	917 (88%)	95 (77%)	278 (84%)	87 (72%)
Systemic	1145 (76%)	90 (70%)	716 (69%)	79 (64%)	221 (67%)	64 (53%)
Other[g]	614 (41%)	29 (23%)	316 (30%)	18 (15%)	102 (31%)	17 (14%)

- **18 to 50 years of age**

After any rMenB+OMV NZ vaccination in a 0-2-6-month schedule, almost all subjects (98%-100%) showed some sign of reactogenicity mainly due to local reactions. After any rMenB+OMV NZ vaccination in a 0-1-2-month schedule, all subjects experienced at least one solicited AE. When comparing the safety profiles of the first two doses in adults to those of the same schedule in adolescents, the reporting rates observed for any solicited AEs as well as for local and systemic AEs were generally similar for adults and adolescents regardless of schedule (Table 56). Similar to the adolescent population, a trend towards decreased reports of solicited AEs with subsequent vaccinations was observed in the adult population, 18 to 40 years of age, at the 0-1-month schedule. Although the sample size is small, similar rates of solicited AEs for the first and second doses were observed with the 0-2-month schedule in adults.

Table 56: Overview of Solicited Adverse Events of rMenB+OMV NZ Vaccine, by Vaccination in Subjects 11 Years of Age and Older, by Schedule

Number (%) of Subjects With Solicited AEs					
		0-1 Schedule[a]		0-2 Schedule[b]	
		18 to 40 yoa[c]	11 to 17 yoa[c]	18 to 50 yoa[c]	11 to 17 yoa[c]
Dose 1		**N=28**	**N=748**	**N=53**	**N=380**
	Any	27 (96%)	705 (94%)	52 (98%)	352 (93%)
	Local	27 (96%)	692 (93%)	52 (98%)	348 (92%)
	Systemic	25 (89%)	574 (77%)	29 (55%)	286 (75%)
	Other[d]	9 (32%)	302 (40%)	13 (25%)	153 (40%)
Dose 2		**N=28**	**N=698**	**N=52**	**N=341**
	Any	25 (89%)	632 (91%)	51 (98%)	306 (90%)
	Local	24 (86%)	621 (89%)	51 (98%)	296 (87%)
	Systemic	20 (71%)	494 (71%)	28 (54%)	222 (65%)
	Other[d]	6 (21%)	216 (31%)	9 (17%)	100 (29%)

8.4.2.2.3. Solicited local AEs in infants and toddlers

- **Infants and toddlers**

The most commonly reported solicited local reaction after each vaccination with rMenB+OMV NZ given concomitantly with routine vaccines was tenderness (65% to 66%) followed by erythema (60% to 64%), and induration (51% to 55%) at 2, 4, and 6 months of age. A higher percentage of subjects receiving rMenB+OMV NZ with concomitantly routine vaccines experienced local reactions than in the group receiving MenC with routine vaccines or receiving routine vaccines alone. Most of these local reactions were transient with few continuing past the day 7 observation window. The majority of reactions were mild or moderate in nature. When comparing percentages of subjects who reported solicited local reactions among the 3 injection sites, the group that received rMenB+OMV NZ with concomitant routine vaccines in a 2, 4, and 6-month schedule had a slightly higher percentage of reactions compared with the routine vaccines alone group. Less than 1% of subjects reported severe local reactions, except for tenderness in which 14% of recipients of rMenB+OMV NZ with concomitant routine vaccines and 11%-12% receiving the combined routine vaccines alone experienced a severe reaction among the 3 doses. For the 2, 3, and 4 months of age schedule, the most commonly reported

solicited local reaction after vaccination with rMenB+OMV NZ and concomitant routine vaccines was erythema (range, 65% to 70%) followed by tenderness (range, 56% to 66%). Solicited local reactions after each InfanrixHexa or Prevenar vaccination were lower in the routine alone vaccination group compared with the rMenB+OMV NZ vaccine given concomitantly routine vaccine group at 2, 3, and 4 months. The most commonly reported local reactions after each Infanrix Hexa and Prevenar vaccination were erythema and tenderness followed by induration and swelling. Most of these local reactions were transient with few continuing past the day 7 observation window. The majority of reactions were mild or moderate in nature. When rMenB+OMV NZ was administered alone in a 2, 4, and 6-month schedule, a slightly lower percentage of subjects reported solicited local reactions as the routine vaccines were given at 3, 5, and 7 months than when it was administered concomitantly with the routine vaccines at the 2, 4 and 6 month and 2, 3, 4-month schedules. The most commonly reported solicited local reaction after vaccination with rMenB+OMV alone was erythema (range, 66% to 67%) followed by tenderness (range, 51% to 60%). Most of these local reactions were transient with few continuing past day 7 observation window. The majority of reactions were mild or moderate in nature.

- **Vaccine naive older infants and toddlers (2-dose schedule)**

After the first and second injections of rMenB+OMV NZ at approximately 6 and 8 months of age, the percentages reporting any solicited local reactions were 93% to 96%. The most common solicited local reactions after the first and second injections were erythema (87% and 89%, respectively) and induration (57% and 60%, respectively). The majority of reactions were mild or moderate in nature; however, 10% [3/30] of recipients reported severe tenderness and 3% [1/30] of recipients reported severe erythema. No subjects reported other severe solicited local reaction. All these reactions were mostly transient with few continuing past the day 7 observation window. Similarly, the most commonly reported local reaction with the two-dose schedule of rMenB+OMV NZ with or without concomitant Priorix-Tetra vaccination in vaccine naïve toddlers at 13 and 15 or 12 and 14 months was erythema and tenderness. Most of these local reactions were transient. The majority of reactions were mild or moderate in nature.

- **Booster dose in toddlers (at 12 months of age)**

The most commonly reported solicited local reaction after vaccination with the fourth (booster) dose of rMenB+OMV NZ with or without concomitant Priorix-Tetra was tenderness (71%) followed by erythema, and induration (66%-68%, and 51%-54%, respectively). Most of these local reactions were transient with few continuing past the day 7 observation window. The majority of reactions were mild or moderate in nature.

- **Booster dose in toddlers (at 26 or 27 months of age)**

The most common local reaction after vaccination with the third (booster) dose was tenderness which was reported in 94% of the subjects with 18% of the subjects having severe tenderness (crying when the injected limb was moved). A total of 70%-76% subjects had erythema with 3% of subjects having severe erythema (>100mm). Other local reactions were induration and swelling.

8.4.2.2.4. Solicited systemic reactions in infants and toddlers

The most commonly reported systemic reaction after vaccination with rMenB+OMV NZ administered at 2, 4, and 6 months of age with routine vaccines was irritability (range, 76% to 79%), followed by sleepiness (range, 53% to 72%), and unusual crying (range, 56% to 69%; Table 57). Percentages of solicited systemic reactions were consistently higher (apart from rash) in subjects administered rMenB+OMV NZ with concomitant vaccines at the 2, 4, 6-month schedule as compared to subjects receiving MenC vaccine with routine vaccines or the routine vaccines alone. Most systemic reactions occurred within the first three days after vaccination

and the majority was transient with few continuing past the day 7 observation window. Most of the reactions were considered mild or moderate in nature.

Table 57: Summary of Solicited Systemic Reactions of rMenB+OMV NZ at a 2, 4 and 6-Month Schedule Given with Concomitant Routine Vaccines, by Vaccination, in Infants

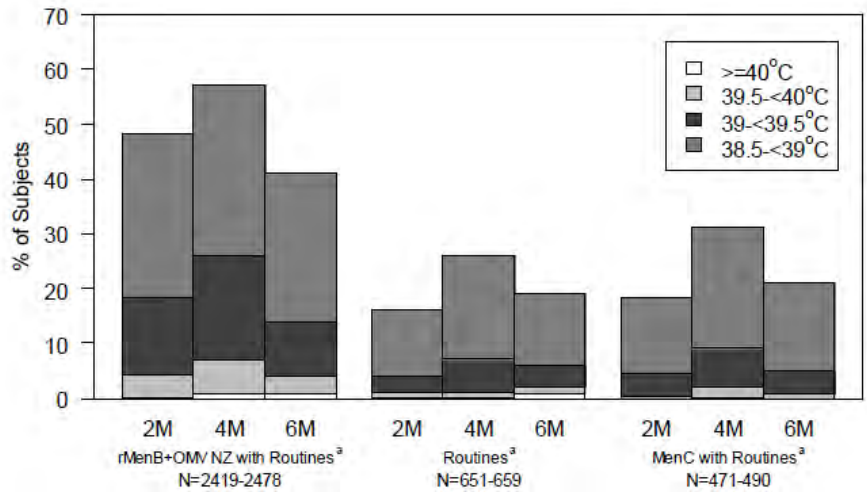
		Number (%) of Subjects With Systemic Reactions				
	Inj. #	MenB+OMV total[a]	MenB+OMV NZ-P12[b]	MenB+OMV NZ-P13[c]	MenC[d]	Routine[e]
N	1	3102	624	2478	490	659
	2	3046-3048	610-612	2436	478-479	654
	3	3023-3024	604-605	2419	470-471	651
Change Eat. Habits	1	1587(51)	352(56)	1235(50)	154(31)	195(30)
	2	1344(44)	308(50)	1036(43)	153(32)	163(25)
	3	1299(43)	284(47)	1015(42)	135(29)	164(25)
Sleepiness	1	2237(72)	416(67)	1821(73)	282(58)	367(56)
	2	1941(64)	395(65)	1546(63)	217(45)	276(42)
	3	1604(53)	329(54)	1275(53)	163(35)	208(32)
Vomiting	1	407(13)	109(17)	298(12)	52(11)	44(7)
	2	383(13)	88(14)	295(12)	52(11)	42(6)
	3	361(12)	95(16)	266(11)	44(9)	47(7)
Diarrhea	1	751(24)	144(23)	607(24)	98(20)	113(17)
	2	661(22)	141(23)	520(21)	74(15)	110(17)
	3	541(18)	126(21)	415(17)	61(13)	81(12)
Irritability	1	2466(79)	459(74)	2007(81)	271(55)	404(61)
	2	2406(79)	449(74)	1957(80)	279(58)	407(62)
	3	2288(76)	431(71)	1857(77)	232(49)	351(54)
Unusual Crying	1	2150(69)	399(64)	1751(71)	254(52)	273(41)
	2	2004(66)	404(66)	1600(66)	237(50)	259(40)
	3	1681(56)	362(60)	1319(55)	181(39)	198(30)
Rash	1	147(5)	30(5)	117(5)	20(4)	23(3)
	2	179(6)	41(7)	138(6)	19(4)	33(5)
	3	154(5)	28(5)	126(5)	16(3)	35(5)
Medically Attended Fever	1	42(1)	19(3)	23(1)	4(1)	6(1)
	2	28(1)	9(1)	19(1)	3(1)	2(<1)
	3	29(1)	10(2)	19(1)	9/472(2)	5(1)
Fever (≥ 38°C)	1	2322(75)	380(61)	1942(78)	226(46)	293(44)
	2	2414(79)	378(62)	2036(84)	304(63)	383(59)
	3	2080(69)	306(51)	1774(73)	196(42)	326(50)

Categorical parameters: N(%), non-categorical parameters: Mean±Std; a MenB+OMV NZ total=combined data of rMenB+OMV NZ (studies V72P12 and V72P13) administered concomitantly with routine vaccines (InfanrixHexa and Prevenar) at: a 2, 4, 6-month schedule ; b MenB+OMV NZ P12=data of rMenB+OMV NZ from study V72P12 administered concomitantly with routine vaccines at a 2, 4, 6-month schedule; c MenB+OMV NZ-P13=data of rMenB+OMV NZ from study V72P13 administered concomitantly with routine vaccines at a 2, 4, 6-month schedule; d MenC=data of Menjugate administered with routine vaccines from study V72P13 at a 2, 4, 6-month schedule; e Routine=data of routine vaccines administered at a 2, 4, 6-month schedule from study V72P13.

Fever (≥38.0°C) was reported by 69% to 79% of subjects after receiving the rMenB+OMV NZ vaccine concomitantly with routine vaccines, compared with 44% to 59% after routine vaccinations only, and 42% to 63% after MenC with concomitant routine vaccines (Table 57). Fever ≥ 40°C was reported by 1% of subjects across the vaccine groups after vaccination. Consistent with the higher fever rates in rMenB+OMV NZ vaccinees, antipyretic usage was also higher in these subjects. Parents were discouraged from using prophylactic antipyretics in both studies V72P12 and V72P13 in order to collect more accurate fever rates. Analyses show that essentially all antipyretics were given after study vaccination, and the majority was given for the treatment of fever. Even though fever rates were higher in subjects vaccinated with rMenB+OMV NZ and routine vaccines, medically attended fever rates were low (1%,) and comparable to recipients of MenC vaccine with routine vaccines and routine vaccines only (<1% to 2%). For all three doses, a higher percentage of subjects reported fever (defined as ≥ 38.0°C) after vaccination with the rMenB+OMV NZ vaccine co-administered with the routine vaccines

compared to the control subjects who received only the routine vaccines, as well as those subjects who received MenC vaccine concomitantly with the routine vaccines. For the rMenB+OMV NZ vaccine group, fever ≥38.0ºC was reported by 78%, 84% and 73% of subjects after doses 1, 2 and 3 respectively, compared with 44%, 59% and 50% of subjects receiving the routine vaccines alone. Most of the fever reported by rMenB+OMV NZ vaccinees was in the 38.0°C to 39.5°C range. After any dose, fever ≥39.5°C was reported by 13.2% of rMenB+OMV NZ vaccinees compared to 4.1% of recipients of the routine vaccines; however, a similar percentage of subjects experienced a maximum temperature of ≥40.0°C after any dose in the rMenB+OMV NZ vaccine group compared to the routine vaccines group (1.7% vs. 1.2%). The incidence of fever was slightly higher with the second dose, and then lower with the third (Figure 15). As such, the fever associated with rMenB+OMV NZ vaccine is very predictable occurring soon after vaccination and is transient with most resolving within 48 hours. In addition, an analysis of fever in study V72P13 showed a trend for subjects to have a higher probability of developing fever at a subsequent dose of rMenB+OMV NZ if the subject experienced fever at the preceding dose(s). Specifically, 87% of the subjects who had fever after the first dose of rMenB+OMV NZ developed fever after the second dose; and 81% of subjects who had fever at both the first and second doses of rMenB+OMV NZ developed fever after the third dose. In comparison, 69.7% of the subjects who had no fever after the first dose of rMenB+OMV NZ developed fever after the second dose; and only 36.7% of subjects who had no fever at both the first and second doses of rMenB+OMV NZ developed fever after the third dose. A similar trend was found for the control subjects vaccinated with either MenC conjugate with routine vaccines or with the routine vaccines alone.

Figure 15: Fever Rates by Dose for rMenB+OMV NZ with Concomitant Routine Vaccines vs. Routine Vaccines Alone vs. MenC with Concomitant Routine Vaccines at a 2, 4, 6-Month Schedule, by Vaccination, in Study V72P13



Solicited systemic reaction rates were similar between the 2, 4, 6-month and 2, 3, 4-month schedules for recipients of rMenB+OMV NZ with routine vaccines. Lower percentages of subjects reported solicited systemic reactions when rMenB+OMV NZ vaccine was administered at 2, 4, 6-month schedule with routine vaccines staggered at 3, 5, and 7 months compared with rMenB+OMV NZ administered concomitantly with routine vaccines in the 2, 4, 6-month and 2, 3, 4-month schedules. Most systemic reactions occurred within the first three days and the majority were transient with few continuing past the day 7 observation window. The majority of reactions were mild or moderate in nature and did not increase with subsequent doses.

- **Older vaccine naive infants and toddlers (2-dose schedule)**

After the first and second injections at 6 and 8 months of age, the percentages reporting at least one solicited systemic reaction were 77% to 82% of subjects in the MenB+OMV NZ group. The

most common solicited systemic reactions were irritability, sleepiness, and change in eating habits. Most systemic reactions occurred within the first three days after vaccination and few were ongoing on day 7. All these reactions were transient with few continuing past the day 7 observation window. The most commonly reported solicited systemic reaction after first and second vaccinations in vaccine naive toddlers with the two- dose schedule of rMenB+OMV NZ was irritability (80% to 81%). Higher percentage of subjects reported solicited systemic AEs in the group who received Priorix-Tetra concomitantly. Most of these reactions were transient with few continuing past the day 7 observation window. The majority of reactions were mild or moderate in nature. In subjects who received rMenB+OMV NZ vaccination at the 13, 15-month schedule (without concomitant Priorix-Tetra vaccination), 36% and 35% of subjects presented with fever (≥38°C) during the 1-4 days after the first and second vaccinations, respectively. In subjects who received rMenB+OMV NZ vaccination at the 12, 14-month schedule with concomitant Priorix-Tetra vaccination at 12 months, similar results were obtained with 37% and 40% subjects presenting with fever (≥38°C) during the 1-4 days after the first and second vaccinations, respectively. When the rMenB+OMV NZ vaccine was concomitantly administered with Priorix-Tetra, 44% of subjects reported fever during the 5-28 days after vaccination (compared to 4% when the rMenB+OMV NZ vaccine was given alone).

- **Booster dose in toddlers (at 12 months of age)**

The most commonly reported systemic reaction after vaccination with the booster dose of rMenB+OMV NZ was irritability (68% when administered with Priorix-Tetra and 73% when administered without Priorix-Tetra) in toddlers who received 3-doses of infant primary series. Similar results were obtained for the systemic reactions to rMenB+OMV NZ vaccine when administered alone or concomitantly with Priorix-Tetra. Most systemic reactions occurred within the first three days and few were ongoing on day 7. The majority of reactions were mild or moderate in nature. Fever (≥38.0°C) from day 1-4 postvaccination was reported by 39% to 41% of subjects receiving a booster dose of rMenB+OMV NZ with or without concomitant Priorix-Tetra at 12 months of age.

- **Booster dose (at 26 or 27 months of age)**

The most common systemic reaction after the booster dose at 26 or 27 months of age was irritability, reported in 60%-82% of the subjects with 1%-6% of the subjects having severe irritability. Other systemic reactions reported were change in eating habits, sleepiness, vomiting, diarrhoea, unusual crying, rash and fever. Most reactions were mild or moderate, and transient. Fever (≥38°C) was reported in 33% of subjects in both groups, with none of the subjects reporting temperature ≥40°C.

8.4.2.2.5. Solicited local reactions in adolescents and adults

Adolescents and adults

- **11 to 17 years of age**

The most commonly reported local reaction was pain (92%-95%), reported by a majority of subjects after each vaccination in both rMenB+OMV NZ and placebo groups. Other common reactions were erythema, swelling and induration. Most of the local reactions, including pain, were mild to moderate in intensity. Severe local reactions were mostly reported as severe pain. Most of these reactions were transient and resolved within the 7-day observation period. Most of the local reactions were reported within the three days after vaccination and resolved within the 7-day observation window. Solicited local reaction profile for the first and second doses of rMenB+OMV NZ vaccine were similar between the 0-1 month and 0-2-month schedule. In the pooled analysis by dose across all schedules a total of 1503 subjects received the first dose of rMenB+OMV NZ vaccine and 1039 received the second dose either in a 0-1 month or a 0-2-month schedule. Similar to the by schedule analysis, pain was still the most commonly reported local reaction in both the rMenB+OMV NZ and the placebo groups, with 91%, 85% and 79% subjects reporting pain after the first, second and third injections in the rMenB+OMV NZ group,

respectively as compared with 86%, 71% and 68% in the placebo group (Table 58). The percentages of subjects reporting pain decreased with subsequent dose. Percentage of subjects reporting severe pain was higher in the rMenB+OMV NZ group than that in the placebo group (13% to 17% vs. 5% to 9%). Incidence rates of erythema, induration and swelling were also higher in the rMenB+OMV NZ group than those in the placebo group; however, few subjects experienced severe reactions. In the 7 days following vaccinations at 6 months, solicited local AEs were reported at similar rates to those reported after the vaccinations of the primary course. Those vaccine groups receiving rMenB+OMV NZ showed higher percentages of subjects with erythema, induration, swelling and pain than the vaccine groups that received placebo at this visit. Most of the solicited local reactions were mild (≤10mm) across all the vaccine groups, and were transient, most resolving within 7days.

Table 58: Summary of Solicited Local Adverse Events of rMenB+OMV NZ Vaccine, by Vaccination in 11 to 17 Years of Age

	Number (%) of Subjects With Injection Site AEs						
		Dose 1		Dose 2		Dose 3	
		rMenB+ OMV NZ[a] N=1503	Placebo[b] N=128	rMenB+ OMV NZ[c] N=1039	Placebo[d] N=124	rMenB+ OMV NZ[e] N=332	Placebo[f] N=121
Erythema	Any	813 (54%)	51 (40%)	535 (51%)	38 (31%)	158 (48%)	35 (29%)
	> 100 mm	2 (<1%)	0	3 (<1%)	0	1 (<1%)	0
Induration	Any	603 (40%)	34 (27%)	415 (40%)	29 (23%)	135 (41%)	14 (12%)
	> 100 mm	2 (<1%)	0	3 (<1%)	0	0	0
Swelling	Any	585 (39%)	25 (20%)	395 (38%)	19 (15%)	129 (39%)	14 (12%)
	> 100 mm	5 (<1%)	0	6 (1%)	0	1 (<1%)	0
Pain	Any	1366 (91%)	110 (86%)	888 (85%)	88 (71%)	261 (79%)	82 (68%)
	Severe	256 (17%)	11 (9%)	151 (15%)	11 (9%)	42 (13%)	6 (5%)

- **18 to 50 years of age**

The most common local reaction after rMenB+OMV NZ vaccination following a 0-2-6-month schedule was injection site pain (96% -100%) with 13% to 18% subjects reporting severe pain. The most common local reaction after rMenB+OMV NZ vaccination following a 0-1-2-month schedule was injection site pain (75% -96%) with 14% to 21% subjects reporting severe pain. The majority of solicited local AEs reported after each vaccination with rMenB+OMV NZ was mild to moderate in severity and transient in duration. The local reaction profile in adults was similar adolescents following rMenB+OMV NZ vaccination. When comparing the adult and the adolescent populations, the percentages of subjects who experienced pain, erythema and induration were similar both within the same schedule groups (0-1-or 0-2-month) and between schedule groups except for erythema in the 0-1-schedule (68% in the adolescents vs. 36% in the adults).

8.4.2.2.6. Solicited systemic reactions in adolescents and adults

- **Adolescents 11-17 years**

The most commonly reported systemic reactions were malaise, myalgia and headache after each vaccination with rMenB+OMV NZ. The rate of the systemic reactions was lower in the placebo group. Most of the subjects reported solicited systemic reactions which were mild to moderate in severity. Severe reactions were reported at a lower frequency and these reactions were transient in duration. Systemic reaction profiles for the first and second doses of rMenB+OMV NZ vaccine were similar between the 0-1-month and 0-2-month schedule. Pooled analysis by dose across all schedule groups showed the same trend in the most commonly reported reactions and the severity of the reactions (Table 59). The incidence rate of the individual systemic reactions was generally higher in the rMenB+OMV NZ group than in the placebo group. A low percentage of subjects reported fever after each dose of rMenB+OMV NZ vaccine and this was comparable to the percentage of placebo subjects reporting fever (3%-5% vs. 2%-4%, respectively). Systemic reactions did not increase with subsequent doses of rMenB+OMV NZ; in fact, the frequency of the two most common reactions, malaise and myalgia,

decreased with subsequent doses. No major difference in the percentages reporting use of analgesic/antipyretic medication was observed after each dose among the different rMenB+OMV NZ dose schedules. Reactions after the booster vaccinations at 6 months occurred at similar rates to those experienced after each of the first two vaccinations in the groups receiving rMenB+OMV at 0, 1 and 6 or 0, 2 and 6 months.

Table 59: Summary of Solicited Systemic Adverse Events and Other Adverse Events, by Vaccination in Subjects 11 to 17 Years of Age Number (%) of Subjects With Systemic AEs

		Number (%) of Subjects With Systemic AEs					
		Dose 1		Dose 2		Dose 3	
		rMenB+OMV NZ[a] N=1503	Placebo[b] N=128	rMenB+OMV NZ[c] N=1039	Placebo[d] N=124	rMenB+OMV NZ[e] N=332	Placebo[f] N=121
Systemic AEs							
Malaise	Any	836 (56%)	62 (48%)	517 (50%)	44 (35%)	147 (44%)	35 (29%)
	Severe	104 (7%)	4 (3%)	74 (7%)	3 (2%)	18 (5%)	1 (1%)
Myalgia	Any	682 (45%)	53 (41%)	418 (40%)	49 (40%)	120 (36%)	34 (28%)
	Severe	98 (7%)	5 (4%)	63 (6%)	4 (3%)	20 (6%)	1 (1%)
Arthralgia	Any	363 (24%)	24 (19%)	222 (21%)	20 (16%)	69 (21%)	15 (12%)
	Severe	29 (2%)	0	35 (3%)	1 (1%)	10 (3%)	0
Headache	Any	691 (46%)	47 (37%)	433 (42%)	41 (33%)	140 (42%)	34 (28%)
	Severe	71 (5%)	2 (2%)	56 (5%)	4 (3%)	18 (5%)	4 (3%)
Nausea	Any	279 (19%)	22 (17%)	166 (16%)	18 (15%)	59 (18%)	19 (16%)
	Severe	21 (1%)	2 (2%)	16 (2%)	1 (1%)	6 (2%)	1 (1%)
Fever	≥38°C	44 (3%)	5 (4%)	41 (4%)	2 (2%)	18/331 (5%)	4 (3%)
	≥ 40°C	1 (1%)	0	0	0	0	0
Med. Att. Fever[g]	Yes	2/1093 (<1%)	1/108 (1%)	1/810 (<1%)	0	0	0
Other Reactions							
Stay Home	Yes	217/1392 (16%)	7/122 (6%)	106/979 (11%)	4/120 (3%)	29/309 (9%)	2/112 (2%)
Analge. Antipyr.[h] Med.Used	Yes	531 (35%)	26 (20%)	277 (27%)	18 (15%)	90 (27%)	17 (14%)
Antipyr. Med.Used[i]	Yes	25/639 (4%)	3/54 (6%)	21/454 (5%)	1/52 (2%)	6/146 (4%)	0

- **18 to 50 years of age**

The most common systemic reactions reported after rMenB+OMV NZ vaccination following a 0-2-6-month schedule were malaise and myalgia. The percentage of subjects reporting malaise, myalgia, arthralgia, and headache increased with subsequent vaccinations. The most common systemic reactions after rMenB+OMV NZ vaccination following a 0-1-2-month schedule were myalgia and headache. Overall, the majority of systemic reactions reported after rMenB+OMV NZ vaccination were mild to moderate in severity and transient in duration. Solicited systemic reactions in adults were less frequent than in adolescents following rMenB+OMV NZ vaccination. When comparing the adult and the adolescent populations, it was observed that the overall tolerability was better in adults than adolescents within the same schedule groups (0-1- or 0-2-month) and between schedule groups. Rates of individual reactions were in general lower in the adults than in the adolescents (Table 60).

Table 60: Summary of Solicited Systemic Adverse Events after Any Vaccination in Subjects 11 Years of Age and Older, by Schedule Number (%) of Subjects With Systemic AEs

		Number (%) of Subjects With Systemic AEs			
		0-1 Schedule[a]		0-2 Schedule[b]	
		18 to 40 yoa[c] N=28	11 to 17 yoa[c] N=748	18 to 50 yoa[c] N=53	11 to 17 yoa[c] N=380
Systemic AEs					
Malaise	Any	6 (21%)	502 (67%)	25 (47%)	248 (65%)
	Severe	1 (4%)	82 (11%)	4 (8%)	45 (12%)
Myalgia	Any	19 (68%)	431 (58%)	25 (47%)	221 (58%)
	Severe	7 (25%)	79 (11%)	4 (8%)	37 (10%)
Arthralgia	Any	8 (29%)	241 (32%)	16 (30%)	121 (32%)
	Severe	1 (4%)	37 (5%)	0	16 (4%)
Headache	Any	14 (50%)	447 (60%)	22 (42%)	207 (54%)
	Severe	2 (7%)	63 (8%)	2 (4%)	33 (9%)
Nausea	Any	7 (25%)	216 (29%)	11 (21%)	99 (26%)
	Severe	0	23 (3%)	2 (4%)	9 (2%)
Chills	Any	11 (39%)	NA	NA	NA
	Severe	2 (7%)	NA	NA	NA
Fatigue	Any	7 (25%)	NA	NA	NA
	Severe	1 (4%)	NA	NA	NA
Fever	≥38°C	2 (7%)	46 (6%)	3 (6%)	27 (7%)
	≥ 40°C	0	1 (<1%)	0	0
Other Reactions					
Stay Home	Yes	8 (29%)	146/705 (21%)	8 (15%)	82/349 (23%)
Analge. Antipyr. Med.Used[d]	Yes	8 (29%)	344 (46%)	15 (28%)	162 (43%)
Antipyr. Med.Used[e]	Yes	NA	22/320 (7%)	NA	17/165 (10%)

8.4.3. Deaths and other serious adverse

Two deaths were reported among adolescent female subjects enrolled into study V72P10 (one was due to craniocerebral trauma and the other suicide). The premature child of one also died within two months after the birth. None of these deaths were assessed to be related to the study vaccination.

8.4.3.1. Infants and toddlers

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%). 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.

8.4.3.2. 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 and none of these AEs were considered to be related to the study vaccination. The majority of SAEs were due to infections or and most of these were moderate in severity. Two AEs in subjects reported as juvenile arthritis were assessed to be possibly/probably related to the study vaccination. On subject in study V72P5 was diagnosed with HIV infection. This SAE was assessed as not related to study vaccination. No SAEs were reported for study V72P4.

8.4.4. Discontinuation due to adverse events

8.4.4.1. Pivotal studies

These have been discussed above.

8.4.4.2. Other studies

These have been discussed above.

8.5. Laboratory tests

Clinical laboratory tests (chemistry, haematology, and routine urinalyses) were carried out on samples provided by participants in study V72P5 before vaccination and 7 days after rMenB+OMV NZ. Of the parameters assessed, three abnormal laboratory values were assessed as clinically significant. These were one case of elevated γGT value (131 U/L) in the rMenB+OMV NZ group, one case of high CRP (25.9, repeat value normal, 2.6) and HIV test positive (SAE). No abnormal laboratory value was assessed as related to the study vaccine.

8.5.1. Liver function

8.5.1.1. Pivotal studies

N/A

8.5.1.2. Other studies

As above

8.5.2. Kidney function

8.5.2.1. Pivotal studies

N/A

8.5.2.2. Other studies

As above

8.5.3. Other clinical chemistry

8.5.3.1. Pivotal studies

N/A

8.5.3.2. Other studies

As above

8.5.4. Haematology

8.5.4.1. Pivotal studies

N/A

8.5.4.2. Other studies

As above

8.6. Post-marketing experience

There is currently no post-marketing experience for rMenB+OMVNZ as the vaccine is not licensed yet. There is some information relevant to the OMV component of the rMenB+OMV NZ vaccine from the experience with OMV-based vaccines used worldwide for the control of local epidemics. It concurs with safety data from clinical trials with OMV vaccines MenBvac and MeNZB and also surveillance data from the vaccination campaign, fever is a characteristic feature of OMV vaccines when administered in the first year of life. The most directly relevant data comes from the New Zealand serogroup B outbreak, where a component of the rMenB+OMV NZ vaccine, as MeNZB, was used to control the clonal outbreak and was intensely studied in post-marketing safety analyses. The results, where self-limited mild to moderate fever was not accompanied by either increased rates of medical attention or, increased rates of

febrile seizures[18,20] are reassuring and will be important to validate in post-marketing studies of rMenB+OMV NZ. Kawasaki Disease was also specifically studied and not found to be increased in frequency after implementation of MeNZB vaccination[21].

8.7. Safety issues with the potential for major regulatory impact

8.7.1. Unwanted immunological events

See Section 8.8

8.8. Other safety issues

8.8.1. Kawasaki disease

There were 7 cases of suspected Kawasaki Disease (KD) reported in clinical studies of rMenB+OMV NZ: 4 cases in Study V72P13, 2 cases in Study V72P12 and 1 case in Study V7213E1. An external, independent KD Expert Panel was organized by Novartis to review the KD cases. The Expert Panel included two paediatric infectious disease physicians and a paediatric cardiologist, all of whom are recognized experts in the KD field. A "confirmed" case of KD was defined by the Expert Panel as one that met the classical case definition of KD: fever of >5 days duration and the presence of at least 4 of the 5 other principal clinical signs (rash, cervical lymphadenopathy, bilateral conjunctiva injection, oral mucosal changes and peripheral extremity changes). Patients whose illness did not meet the KD case definition, but who had coronary artery abnormalities consistent with KD were also classified as a confirmed case. Patients whose illness did not meet the above KD case definition and had no coronary artery abnormalities were classified as having "incomplete" KD. For these cases, additional clinical and laboratory findings were taken into consideration to judge the case as a "likely or probable" case of KD or "unlikely" KD. The Expert Panel was also asked to judge the causal relationship of the cases as either "unrelated" or "possibly related" to study vaccinations. The Expert Panel utilized the concept of a latency period of up to 30 days between the time of study vaccination and onset of fever as an aid in determining whether the case could be considered related to study vaccination.

The first two suspected KD cases were judged to be unrelated to study vaccination by the investigators. The Expert Panel considered both these cases from Finland as confirmed cases of KD. One was assessed as unlikely to be related to study vaccination due to the 7-week interval between study vaccination and onset of symptoms. The causal relationship of the other could not be ruled out since the 3-week interval between study vaccination and onset of symptoms was considered to be within the latent period of KD.

Two additional suspected KD cases were reported from Study V72P13. Both cases were judged to be unrelated to study vaccination by the investigators. One was 5½ months post-vaccination and the other did not fulfil the case definition for KD (fever plus only 3 of 5 principal clinical findings met), and was considered a case of incomplete KD. However, based on other findings they judged it as an incomplete, but probable KD case.

The third and fourth cases of KD occurred in 2009 in male Belgian subjects participating in open-label Study V72P12. Both cases were judged to be possibly related to study vaccination by the investigators. One was considered an "unlikely" case of KD and the illness started prior to study vaccination (fever, elevated platelets and CRP) and therefore the event was considered

[20] Stehr-Greena P, Radkea S, Kieft C, Gallowaya Y, McNicholas A, and Reid S. The risk of simple febrile seizures after immunisation with a new group B meningococcal vaccine, New Zealand. *Vaccine* 2008; 26:739-742.
[21] McNicholas A, GallowayY, Stehr-Green P, Reid S, Radke S, Sexton K, Kieft C, Macdonald C, Neutze J, Drake R, Isaac D, O'Donnell M, Tatley M, Oster P, and O'Hallahan J. Post-Marketing Safety Monitoring of a New Group B Meningococcal Vaccine in New Zealand, 2004–2006. *Human Vaccines*, 2007; 3:5, 196-204.

unrelated to study vaccination. The other Belgian case met the clinical criteria for KD and had a symptom onset 3 weeks post study vaccination and, as a result, the case could not be ruled out for causal relationship based on this latent period. This subject received rMenB+OMV NZ co-administered with rotavirus vaccine.

The seventh suspected case of KD occurred in a 20-month-old male subject participating in extension study V72P13E1 in the Czech Republic. He received Priorix-Tetra at 12 months of age, and two injections of rMenB+OMV NZ vaccine at 13 and 15 months of age. The Expert Panel adjudicated this case as an incomplete, but likely case of KD and judged it as unrelated to study vaccination due to the long interval between the onset of symptoms and study vaccination.

The time to onset after study vaccination is also inconsistent with a causal relation with rMenB+OMV NZ. The time of onset for the six cases in recipients of the rMenB+OMV NZ vaccine was 1 day (or less), 3 weeks, 3 weeks, 7 weeks, 3½ months, and 4½ months, respectively. The one case in the control subject receiving MenC conjugate occurred 5½ months after vaccination. The wide range of onset intervals suggests a lack of causal linkage to study vaccination. Only two of the three confirmed cases of KD following vaccination with rMenB+OMV NZ occurred within the 30-day post vaccination risk window. The only other case that occurred within the 30-day period was the event adjudicated as unlikely to be KD. If the confirmed KD cases and the incomplete, but likely KD case are considered, the total number of KD cases occurring in infants at any time interval for studies V72P12 and V72P13 was 4 for the rMenB+OMV NZ recipients (0.1%) vs. 1 for the control recipients (0.07%). Thus, the frequency of KD cases (confirmed or likely) is similar between recipients of rMenB+OMV NZ and the control subjects (0.1% vs. 0.07%).

Based on the cumulative total of 2,915 person-years of follow-up time for the rMenB+OMV NZ vaccinees in both studies V72P12 and V72P13, the estimated (equivalent) annual incidence of KD is 137 [95% CI: (37, 351)] per 100,000 children when the four confirmed and incomplete KD cases are considered, 103 [95% CI: (21, 301)] per 100,000 when only the 3 confirmed cases are considered, and 69 [95% CI: (8, 248)] per 100,000 when only the two confirmed and possibly related cases are considered (within the 30-day period after vaccination). In comparison, the estimated (equivalent) annual incidence rate for the confirmed KD case in the control arms, based on 1,529 person-years of follow-up time (subjects receiving MenC conjugate co-administered with routine vaccines or routine vaccines only), is 65 [95% CI: (2, 364)] per 100,000 children. The point estimates are similar with very wide confidence intervals and overlapping, indicating that there are no significant differences in KD incidence rates between the rMenB+OMV NZ and control groups.

8.8.2. Fever

There was a high rate of mild-moderate local and systemic side effect particularly high rates of fever, when co-administered with routine childhood vaccinations. There is an ongoing Study V72P16, included in the submission. The aim of this study was to assess whether prophylactic administration of antipyretics could decrease the incidence of febrile reactions associated with rMenB+OMV NZ vaccination co-administered with InfanrixHexa and Prevenar at 2, 3 and 4 months of age. Subjects received one dose of paracetamol just before each study vaccination and two further doses at 4-6 hour intervals after vaccination. The impact of prophylactic antipyretics on the immune response to rMenB+OMV NZ and the routine vaccines was also investigated in the study. An interim analysis of the fever rates following the three-dose primary series has been performed and is presented in Table 61 below. The results show that prophylactic paracetamol reduced the percentage of subjects reporting fever after any dose (fever ≥ 38.0°C from 88% to 76%, and fever ≥ 38.5°C and ≥ 39.0°C was reduced from 69% to 39% and 30% to 13% of subjects, respectively. Prophylactic paracetamol had no clinically significant impact on the immune response to rMenB+OMV NZ or to the antigens in the routine vaccines InfanrixHexa and Prevenar).

Table 61: Summary of Body Temperature After Vaccination (Any Dose) with rMenB+OMV NZ with Concomitant Routine Vaccines at 2, 3 and 4 Months of Age in Study V72P16 – Evaluation of Prophylactic Paracetamol Given Prior to Each Dose

	rMenB+OMV NZ + Routine Vaccines *Non-Prophylactic Antipyretic*[a]	rMenB+OMV NZ + Routine Vaccines *Prophylactic Paracetamol*[b]
	N=184	N=183
Max. Rectal Temp.(°C):		
<38°C	22(12%)	44(24%)
38 - 38.4°C	35(19%)	66(36%)
38.5 - 38.9°C	72(39%)	48(26%)
39 - 39.4°C	40(22%)	17(9%)
39.5 - 39.9°C	14(8%)	5(3%)
≥40°C	1(<1%)	1(<1%)
Max. Temp. by Grade:		
Mild - (38.5-39.4°C) Grade 1	112(61%)	66(36%)
Moderate - (39.5-40.4°C) Grade 2	15(8%)	6(3%)
Temp ≥38°C:		
Yes	162(88%)	139(76%)
No	22(12%)	44(24%)
Temp ≥38.5°C:		
Yes	127(69%)	72(39%)

8.8.3. Seizures

8.8.3.1. Study V72P13

Overall, a total of 15 subjects in Study V72P13 experienced febrile or non-febrile seizures following study vaccinations: 13 who received rMenB+OMV NZ with routine vaccines, and 2 who received either MenC conjugate vaccine co-administered with routine vaccines or routine vaccines only in the control groups. Seizures were reported as serious adverse events in 13 of the 15 subjects. Febrile seizures were reported in 2 subjects within 24 hours and 6 subjects overall after receiving rMenB+OMV NZ. No febrile seizures were reported in the control subjects. Two subjects experienced febrile seizures at 4 months of age within 24 hours of vaccination with second doses of rMenB+OMV NZ, InfanrixHexa and Prevenar. These events were judged by the investigators as probably related to study vaccination. One of these subjects had a complex febrile seizure and was discovered after enrolment to have significant underlying neurologic pathology with developmental delay. This subject was withdrawn from the study and subsequently experienced another apparent febrile seizure 5 months after this event. The

four other febrile seizure cases were considered unrelated to study vaccination with rMenB+OMV NZ, InfanrixHexa and Prevenar. These events occurred anywhere from 15 days to 6 months after the third dose, beyond the onset of fever associated with study vaccination. In each of these cases, fever could be attributed to a concurrent illness. All six of the cases of febrile seizure were transient and resolved completely. With the exception of the subject with underlying neurologic pathology developmental delay, no further seizures were reported in the other subjects.

Non-febrile seizures were reported in nine subjects. 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. An independent, expert paediatric neurologist has reviewed the cases and advised that the event in one subject was not a seizure, but most likely a benign myoclonus. 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 third dose and, as such, were all judged by the investigators to be unrelated to study vaccination.

8.8.3.2. Study V72P12

A total of 10 subjects experienced febrile or non-febrile seizures following vaccinations: 5 events following study vaccination with rMenB+OMV NZ administered with routine vaccines or rMenB+OMV NZ given alone, and 5 events following routine vaccines only. Seizures were reported as serious adverse events in 8 of the 10 subjects. Febrile seizures were reported in four subjects. One 4-month-old subject experienced a febrile seizure at 2 days after the second dose of rMenB+OMV NZ given separately. This event was judged by the investigator as possibly related to study vaccination. The three other cases of febrile seizure occurred with a latency of between 109 and 186 days after the third vaccination, well beyond the duration of fever associated with the study vaccinations. One occurred following the third vaccination with rMenB+OMV NZ with routine vaccines and two occurred following the third vaccinations with InfanrixHexa and Prevenar. None of the events were considered by the investigator related to study vaccination. No further febrile seizures were reported in the four subjects reviewed above.

Six non-febrile seizures were reported. Two cases of convulsion/epilepsy occurred on the same day as the first vaccinations with rMenB+OMV NZ, InfanrixHexa and Prevenar or rMenB+OMV NZ alone. One case was reviewed by an outside expert paediatric neurologist, and thought to be a benign or sleep myoclonus, rather than a seizure. The other was judged by the investigator as possibly related to the investigational vaccine and was considered moderate in severity; the subject recovered completely with no sequelae. Two cases, reported as epilepsy and petit mal epilepsy, were temporally related to vaccination with the routine vaccines, occurring on the same day or one day after the vaccinations with InfanrixHexa and Prevenar. Both events were judged as possibly related to the study vaccinations and the subjects were reported to have recovered. One of these was also thought not to be a seizure, but probable sleep myoclonus. Of the remaining two non-febrile seizure cases, one occurred on day 178 after the third immunizations with rMenB+OMV NZ and routine vaccines and was judged as unrelated to the study vaccinations by the investigator; the child was subsequently diagnosed with a ganglioglioma. The last case, reported as epilepsy, occurred on day 73 after the third immunizations with the routine vaccines. This event was judged as unrelated to study vaccination.

8.8.3.3. Integrated analysis of seizures in studies V72P12 and V72P13

Of the 10 febrile seizures and 15 non-febrile seizures from Studies V72P12 and V72P13, three was not thought to be seizures when reviewed, but are included in the analysis. Three febrile

seizures were reported within 2 days of vaccination with rMenB+OMV NZ; in two cases rMenB+OMV NZ was co-administered with InfanrixHexa and Prevenar and in one case rMenB+OMV NZ was given alone. One of these subjects had a pre-existing neurological condition. In total, 8 recipients of rMenB+OMV NZ vaccine (0.7 events/1000 doses) vs. 2 recipients of control vaccines (0.3 events/1000 doses) were reported to have febrile seizures in studies V72P12 and V72P13.

Six non-febrile seizures were reported within 14 days of vaccination: 4 cases occurred after rMenB+OMV NZ vaccination and two cases were in the control group representing event rates of 0.3/1000 doses and 0.3/1000 doses, respectively. There were 9 additional non-febrile seizures that were reported greater than 14 days after vaccination: 6 cases (0.5/1000 doses) in rMenB+OMV NZ vaccinees vs. 3 in control subjects (0.5/1000 doses). In total, independent of time interval, the rate of non-febrile seizures was similar between the two treatment groups (0.8/1000 doses vs. 0.8/1000 doses). Similar rates of events are observed across the time intervals for the two treatment groups. There were 7 events temporally associated with rMenB+OMV NZ vaccination (within 2 days of vaccination) compared to 2 events in control subjects in the same time period; the calculated rates are 0.59 events/1000 doses of rMenB+OMV NZ administered (95% CI: [0.24, 1.21]) vs. 0.33 events/1000 doses of control vaccine administered (95% CI: [0.04, 1.18]). The overlapping CIs indicate no statistically significant difference in the rates.

Based on person-years of follow-up time for the recipients of rMenB+OMV NZ and recipients of the control vaccines, the expected number of febrile seizures and non-febrile seizures was calculated (Table 62). The number of febrile seizures was based on two publications[22,23] and the number of non-febrile seizures was estimated from one publication[21]. The number of febrile seizures that was observed in Studies V72P12 and V72P13 is within the expected range for both treatment groups. The number of nonfebrile seizures that were observed for both treatment groups is consistent with what would have been expected in this population.

Table 62: Observed vs. Expected Number of Cases of Febrile and Non-Febrile Seizures in Studies V72P12 and V72P13

		Febrile Seizures		Non-Febrile Seizures	
Group	**Person-Years of Follow-up Time**	**Observed**	**Expected***	**Observed**	**Expected+**
rMenB+OMV NZ	2,915	8	11 to 12	10	10
Control	1,529	2	6	5	5

*Calculations based on two published febrile seizure incidence rates in children <12 months of age: 3.7/1000 and 4.1/1000; + Calculations based on non-febrile seizure incidence rate of 3.3/1000 in children <12 months of age.

8.8.3.4. Study V72P13E1

All subjects enrolled into V72P13E1 extension study were to receive rMenB+OMV NZ, either alone or with MMRV at some time during the study. A total of 18 subjects experienced febrile or non-febrile seizures following vaccinations: 7 events following study vaccination with rMenB+OMV NZ administered with or without Priorix-Tetra, and 11 events following Priorix-Tetra vaccination only or other routine vaccine(s) that were administered during the study. Seizures were reported as serious adverse events in 11 of the 18 subjects. In rMenB+OMV NZ vaccination groups, two events (one febrile convulsion and one convulsion) were judged as possibly related to study vaccination; both subjects recovered completely. Following immunization with Priorix-Tetra or other routine vaccines given during the study, none of the events were judged to be possibly or probably related to study vaccination.

[22] Van de Berg B. J, Yerushamy J. Studies on convulsive disorders in young children. *Pediat Res* 1969; 3:298-304.
[23] Verity C.M, Bulter N.R, Golding J: Febrile convulsion in a national cohort followed up from birth. I-Prevalence and recurrence in the first five years of life. *British Medical J* 1985.

8.8.3.5. Febrile seizures relative to day of last study vaccination in toddlers

- **Day 1 to day 2**

Febrile seizures were reported in 12 subjects. Two febrile seizures were reported within the 2-day interval after the administration of routine vaccines. One of these events occurred on the same day as vaccination with the routine vaccines Prevenar, InfanrixHexa and MenC conjugate and the other occurred one day after vaccination with Prevenar and InfanrixHexa. The latter case was attributed to a concurrent Salmonella gastroenteritis.

- **Day 3 to day 14**

Four febrile seizures were reported in the study day 3 to 14 time interval, all of which occurred following vaccination with rMenB+OMV NZ (with or without Priorix-Tetra). One 12-month-old subject experienced a febrile seizure at 9 days after rMenB+OMV NZ given concomitantly with Priorix-Tetra. This event was judged by the investigator as possibly related to study vaccination (possibly related to Priorix-Tetra as the time interval was plausible for live-attenuated vaccines). Two other cases occurred 10 days after vaccination with rMenB+OMV NZ alone or rMenB+OMV NZ with Priorix-Tetra. Both events were judged as not related to study vaccination by the investigators. The fourth febrile seizure event in the day 3-14 time interval occurred 7 days after routine vaccination with InfanrixHexa and Prevenar.

- **Day 15 or later**

The 6 remaining cases of febrile seizure occurred greater than 14 days after study vaccination. Three followed concomitant vaccination of a booster dose rMenB+OMV NZ with Priorix-Tetra; all were considered unrelated to study vaccination as the events occurred anywhere from study day 20 to 46 after the rMenB+OMV NZ doses, which are beyond the duration of fever associated with rMenB+OMV NZ vaccination. The 3 other febrile seizures followed vaccination with Priorix-Tetra, influenza vaccine or InfanrixHexa and Prevenar, and all were judged as not related causally as the events occurred anywhere from 42 to 102 days after vaccination.

8.8.3.6. Non-febrile seizures

Six non-febrile seizures were reported. Only one event occurred in the day 1-2 interval following study vaccination. This was reported as a convulsion which occurred on the same day as the subject's first vaccination with rMenB+OMV NZ (subject **Information redacted**). The event was judged by the investigator as possibly related to the investigational vaccine, but was considered mild and non-serious; the subject recovered completely with no sequelae. No other non-febrile seizures occurred where the preceding vaccination was with rMenB+OMV NZ. The remaining five non-febrile seizures occurred after vaccination with Priorix-Tetra, influenza vaccine or InfanrixHexa and Prevenar (proximal preceding vaccination to the event). These events were considered unrelated to study vaccination and occurred from 10 to 53 days after vaccination.

8.8.4. Hypotonic-Hyporesponsive Episodes

There were two cases of hypotonic-hyporesponsive episode (HHE) reported as serious adverse events in study V72P12 and no HHE cases reported in study V72P13. In addition, there were two cases of hypotonia reported as serious adverse events, one each in studies V72P12 and V72P13. In one, from study V72P13 the hypotonia event occurred 3 months after the third vaccination with MenC conjugate co-administered with routine vaccines and was not thought to be related. The other three events in subjects from study V72P12 occurred within the 48-hour risk window and were evaluated as suspected cases of HHE based on the Brighton case definition (M. Buettcher et al., 2007). On (study V72P12) occurred two days after the third dose of rMenB+OMV NZ co-administered with InfanrixHexa and Prevenar. The event lasted a few hours and the subject completely recovered and was thought to be possibly related to study vaccination. Because only hyporesponsiveness was reported for the subject (no hypotonia,

pallor or cyanosis), the event did not meet the case definition for HHE. The other case in study V72P12, met the case definition of HHE. The event occurred within 1 day after the second vaccination with rMenB+OMV NZ coadministered with InfanrixHexa and Prevenar and, as such, was judged as possibly related to study vaccination. The event lasted less than 5 minutes and the subject completely recovered. The other case (study V72P12)was reported as an episode of muscle hypotonia; however, the event did meet the case definition of HHE (Brighton Level 1 diagnostic certainty) based on the triad of hypotonia, pallor, and hyporesponsiveness (not reacting to mother, apathy). The event occurred 6 hours after vaccination with the routine vaccines InfanrixHexa and Prevenar. The hypotonia resolved the same day as vaccination and the subject was subsequently discharged from the hospital in good health.

8.8.5. Use in pregnancy

Pregnancy was an exclusion criterion in all clinical trials. However, 19 pregnancies in study V72P10 were reported during the study period and another two during studies V72P4 and V72P5. Study V72P10: 19 pregnancies were recorded and none of the subjects reported spontaneous abortions. All these subjects had a live-born delivery except in one subject ([**Information redacted**]) in whom the outcome was unknown. Two subjects had given birth to the infants with congenital abnormalities. There were no other reports of adverse pregnancy outcomes recorded during the study. Study V72P4: One subject was confirmed pregnant on day 86 (23 days after second vaccination) and withdrew her consent. This pregnancy resulted in a live birth and the infant did not present congenital abnormality. Study V72P5: One subject became pregnant 5 months after the last vaccine dose (rMenB+OMV NW). This pregnancy resulted in a live natural birth and the infant did not present congenital abnormality.

8.9. Evaluator's overall conclusions on clinical safety

This vaccine has a very high incidence of local reactions at the injection site of rMenB+OMV NZ. These consisted of tenderness, erythema and induration. Overall, most of the local reactions were transient and resolved within the 7 day observation window. The majority of reactions were mild or moderate in nature. Other than for tenderness, severe local reactions were infrequent at the rMenB+OMV NZ injection site. In infants and toddlers, a slightly lower percentage of subjects reported solicited local reactions at the injection site of rMenB+OMV NZ when it was given alone at 2, 4 and 6 months (routine vaccines at 3, 5 and 7 months) than when it was administered concomitantly with the routine vaccines, whether at the 2, 3 and 4 month or 2, 4, 6-month schedules. rMenB+OMV NZ elicited higher local reactions rates compared with MenC vaccine and the routine vaccines InfanrixHexa and Prevenar. Local reaction rates for rMenB+OMV NZ were common in all age groups studied and didn't vary much according to the number of the vaccination in the schedule.

Solicited systemic reactions were extremely common in infants and toddlers following vaccination with rMenB+OMV NZ. Percentages for solicited systemic reactions were higher (apart from rash) in infants administered rMenB+OMV NZ concomitantly with routine vaccines at the 2, 4, 6-month schedule (up to 86%) compared to those subjects receiving MenC vaccine with routine vaccines or routine vaccines alone. Most of the systemic reactions occurred within the first three days and were transient with few continuing past the day 7 observation window. The majority of reactions were mild or moderate in nature. As for the local reactions, there was no apparent cumulative effect of the booster dose of rMenB+OMV NZ. Of note, in infants, the highest rate of fever after rMenB+OMV NZ was observed at 6 hours post-vaccination (day 1) and its duration was transient, resolving for most of the subjects by 48 hours after vaccination on day 3.

This is discussed further in the following section, but this very high incidence of fever, has implications both for medical practitioner recommendations in terms of infant vaccination scheduling and patient (or parent) acceptance. Options to lower the incidence of fever include

the prophylactic use of anti-pyretics (being examined in study V72P16 which is ongoing but looks to be effective according to a preliminary report) or by alternating the administration of rMenB+OMV NZ and other routine childhood vaccinations. It will be important that the incidence of fever is explicitly discussed by medical practitioners with patients (parents) prior to administration. It also has implications for the incidence of febrile convulsions, given the age group at risk for these. In infants with a history of febrile convulsions, it may be worth taking special measures to lower the risk of fever (separation from other vaccines and the use of anti-pyretics).

There are also a number of other adverse events of significance reported in the infant studies. These are KD, hypotonic episodes and both febrile and non-febrile seizures (discussed in Section 8.8). The few KD cases that occurred in the rMenB+OMV NZ clinical studies do not allow a definitive assessment of the causal relationship between rMenB+OMV NZ vaccination and KD. Furthermore, the co-administration of rMenB+OMV NZ with other vaccines is a confounding factor in many of the cases. It is similar for the other conditions (discussed above). Although these may not be causally related to the vaccine (or even occur in a higher than normal incidence in the studies) but do warrant further attention in the post-marketing studies (also discussed below).

9. First round benefit-risk assessment

9.1. Assessment of benefits

The benefits of rMenB+OMV NZ in the proposed usage are:

- This appears to be a vaccine that will provide broad coverage against the diverse strains of serogroup B *N. meningitidis*. The vaccine induces robust immune responses in individuals of all ages. In infants, a 3-dose regimen beginning at age 2 months induces a bactericidal antibody titer that correlates with protection against strains containing the vaccine antigens in 79% to 100% of vaccinees (assessed one month post-primary vaccination course). In older infants, toddlers, adolescents, and adults, 2 doses of the vaccine given at 1 to 2 month intervals induces protective bactericidal antibody titres against the strains containing the vaccine antigens in nearly 100% of subjects. In toddlers, persistence of antibodies has been shown at 12 months post-vaccination.
- There is very limited data on functional immune response against NHBA given that a suitable reference strain for evaluating NHBA-specific bactericidal killing (strain M10713) was identified late in the development program and has only been used in a subset of participants in Study V72P13 and Study V72P13E1 (prior to this an ELISA test was used as a surrogate).
- It appears that this vaccine can be given either concurrently with or interspersed between other routine infant and toddler vaccines. The immune responses to antigens of the concomitantly administered vaccines were generally similar when given with rMenB+OMV NZ or alone.
- The proportion of subjects experiencing systemic reactions, unsolicited adverse events, and serious adverse events were generally similar across groups. For infants, the rates of local and systemic reactions, including fever, were higher in the recipients of rMenB+OMV NZ when given concomitantly with routine vaccines as compared with recipients of routine vaccines alone. However, most of these events were categorized as mild or moderate, were transient, and did not lead to increased rates of health care utilization or specific medical sequelae. Further, when the rMenB+OMV NZ vaccine was given separately from routine vaccines, the rates of local and systemic reactions appeared similar in both groups. These

data support administration of rMenB+OMV NZ alone or concomitantly with routine paediatric vaccines.

9.2. Assessment of risks

The risks of rMenB+OMV NZ vaccine in the proposed usage are:

- There is a potential issue that it doesn't cover the circulating serotypes. Although we have some good data from the MATS tests done by Novartis indicating that this is will be effective against the majority of *N. meningitidis* serotypes, this was done on 150 isolates. It will be important to do ongoing laboratory and clinical data collection to assess its appropriateness to circulating serotypes.
- It has a high incidence of mild-moderate side effects, particularly in infants, although these were not judged to be serious and they resolved quickly. Local reactions such as pain, erythema were experienced by the majority of recipients. Fever and malaise were also very common, although these generally resolved quickly. There was a very high incidence of fever occurring the day after vaccination, particularly when rMenB+OMV NZ was co-administered with routine childhood vaccinations.
- It has a low incidence of significant adverse events but it will be important to continue to monitor these in order to be able to detect any causal relationship to Kawasaki disease and seizures (not found in the data supplied in this application).

9.3. Assessment of benefit-risk balance

The benefit-risk balance of rMenB+OMV NZ vaccine, given the proposed usage, is favourable.

Invasive meningococcal disease can be a severe illness associated with a high case fatality rate, and a high percentage of survivors suffering from permanent neurologic and other sequelae. In Australia the proportion of meningococcal disease cases caused by serogroup B is relatively high, accounting for approximately 80% of all cases. However, unlike serogroups A, C, W, and Y, there is currently no effective vaccine that protects against serogroup B meningococcal disease. The disease most commonly affects infants below 1 year of age.

The rMenB+OMV NZ vaccine has been developed based on proven efficacy of OMV-based vaccines and on the use of antigens which are conserved and appears to be highly effective in inducing bactericidal antibodies in humans beginning from 2 months of age. These studies have shown a high level of efficacy at 1 month following primary course of vaccination. There is also data showing persistence of antibodies 12 months after the primary course in infants and toddlers. One caveat to this is the fact that NHBA-specific bactericidal killing was only directly assessed in a small subset of participants in V72P13/ V72P13E1.

The high rate of mild-moderate local and systemic side effects particularly the high rates of fever, when co-administered with routine childhood vaccinations, that I have mentioned above, was also raised as a concern by the EMEA and Novartis has responded that they feel that the context and the benefit to be seen from using the vaccine far outweighs this problem. In fact, they responded to specific queries regarding this with the following statement, "*Fever associated with rMenB+OMV NZ vaccine given concomitantly with routine vaccinations is predictable, mild-to-moderate in severity, transient, and when properly communicated does not result in an increased frequency of medical evaluations."* This has merit, although will need to be clearly articulated to recipients (or parents of recipients) prior to administration with appropriate instruction about how to manage.

Another option to reduce the possibility of postvaccination fever is through the use of prophylactic antipyretics. The results of Study V72P16 show that prophylactic paracetamol reduced the percentage of subjects reporting fever after any dose (fever ≥ 38.0°C) from 88% to

76%, and fever ≥ 38.5°C and ≥ 39.0°C was reduced from 69% to 39% and 30% to 13% of subjects, respectively. Prophylactic paracetamol had no clinically significant impact on the immune response to rMenB+OMV NZ or to the antigens in the routine vaccines InfanrixHexa and Prevenar).

So the major options in terms of reducing the rate of fever appear to be either separating the administration of rMenB+OMV NZ from the administration of routine childhood vaccinations or giving prophylactic anti-pyretics.

There is also a response to the concern about febrile seizures also raised by the EMEA. Three febrile seizures were reported within 2 days of vaccination with rMenB+OMV NZ; in two cases, rMenB+OMV NZ was co-administered with InfanrixHexa and Prevenar and in one case rMenB+OMV NZ was given alone. These events can be considered within the risk window for the post vaccination fever associated with rMenB+OMV NZ. One of these subjects had a complex febrile seizure and was discovered after enrolment to have significant underlying neurologic pathology with developmental delay. This subject was withdrawn from the study and subsequently experienced another apparent febrile seizure 5 months after this event. In response, Novartis states that, 'Based on these small number of cases, no definitive conclusions can be made with respect to increased risk of febrile seizure associated rMenB+OMV NZ vaccination in infants. There was no evidence from these studies, however, of an increased risk of febrile seizures following rMenB+OMV NZ vaccination. Some additional assurance can be gained from Study V72P13E1, in which no febrile seizures were reported within 9 days of vaccination of over 2200 toddlers with rMenB+OMV NZ. This is notable since febrile seizures are at a peak in the toddler age group.

This assessment may currently be accurate, but more evidence in support of the absence of any excess attributable risk of febrile seizures needs large-scale post-marketing studies. Also, given the incidence of seizures and in particular febrile convulsions seen in these studies, I would recommend that either of these as pre-existing conditions would constitute a relative contra-indication to vaccination with this vaccine.

The EMEA also requested further responses in relation to the cases of KD seen in the studies. There was a panel of experts convened to assess all the reported cases and their relationship to study vaccine. Three cases occurred more than 30 days after vaccination and hence were thought unlikely to be related. One of the cases occurring within 30 days was thought unlikely to be KD. Hence there were two cases meeting the case definition of KD occurring within 30 days of vaccination. These are summarised below in Table 63.

Table 63: Summary of Suspected Cases of Kawasaki Disease in Studies V72P12 and V72P13 by Onset Interval ≤ 30 Days and > 30 Days from Last Dose of Study Vaccine

	Onset Interval from Last Study Vaccination	
Adjudication Outcome	≤ 30 days	> 30 days
rMenB+OMV NZ (N=4050*)		
Confirmed KD	2 (0.05%)	1 (0.02%)
Incomplete but likely KD	0	1 (0.02%)
Unlikely KD	1 (0.02%)	0
MenC or Routine Vaccines (N=1461*)		
Confirmed KD	0	1 (0.07%)

The incidence rates of KD in studies V72P12 and V72P13 appear to be higher than estimates obtained from other sources. But annual incidence rates in children < 1 year of age are available for only a few selected European countries. Denmark, Finland and Ireland have estimated

annual incidence rates of 4.5, 12 and 19.7 cases, respectively, per 100,000 children <1 year of age[24, 25]. So, given the very low numbers, interpretation of these differences is difficult. An important consideration is the very small population sizes and number of KD cases in the rMenB+OMV NZ studies, resulting in highly unstable point estimates and wide confidence intervals. Also, the age group studied – infants <12 months of age – have the highest incidence rates of KD, and are not always reported.

In their response, Novartis also reports that three vaccines that have been licensed for use in U.S. infants in the past decade – Prevnar, Rotateq, and Rotarix – were all associated with higher rates of KD in comparison to controls during pivotal studies, which led to the requirement of detecting KD as a specific outcome of interest in large-scale post-marketing safety studies. It may be that the elevated rates of KD observed in clinical studies of rMenB+OMV NZ and other recently licensed paediatric vaccines most likely reflect enhanced and complete case detection, including detection of incomplete KD cases as well. Novartis states that there 'is currently no clear evidence to support a causal relationship between KD and rMenB+OMV NZ vaccination. As such, Novartis does not believe that the observed KD cases affect the safety of rMenB+OMV NZ vaccine nor do they impact the evaluation of the risk/benefit of the product. As with other recently launched paediatric vaccines, Novartis does acknowledge that KD should be followed as an outcome of interest in large-scale post-marketing safety studies of rMenB+OMV.' Obviously this needs to be seriously and properly followed in large post-marketing studies of this vaccine as well.

10. First round recommendation regarding authorisation

Approval is recommended subject to definitive information regarding the post-marketing studies relating to the safety issues raised above. These 'enhanced pharmacovigilance' studies are necessary to provide assessment of specific adverse events. Also, the Australian MATS data is currently very limited and only available for 172 specimens collected between 2009-2011. This should be extended and more data provided to confirm the likely relevance of the vaccine serotypes in Australia. Post-marketing studies will also be necessary to demonstrate the clinical effectiveness of the vaccine in settings with high population coverage. The other responses to specific EMEA questions (mainly relating to technical aspects of the immunogenicity testing and clarification of study design are also noted).

11. Clinical questions

The clinical evaluator did not raise any questions in relation to the evaluated clinical data.

12. Supplementary clinical evaluation

12.1. Background

In order to address TGA concerns about the absence of real-time or accelerated stability data, the sponsor claimed that clinical data from two studies, V72P16 and V72_41, provide interim evidence of the potency of the vaccine and acceptably low endotoxin levels over the duration of the proposed shelf-life as follows:

[24] Fischer et al., KD incidence in Finland. *Pediatr. Infect. Dis*. J. 2007; 26:411-415.
[25] Lynch M., Holman R.C., Mulligan A., et al: Kawasaki syndrome hospitalizations in Ireland, 1996-2000. *Pediatr. Infect. Dis. J.* 2003; 22:959-962.

- Vaccine lots used beyond their proposed 24-month shelf-life have been shown to be clinically effective:
  - An old Lot was used at a median age of 27 months in clinical Study V72P16 and gave an acceptable protective immune response.
  - Another Lot had a median age of 29 months when used in clinical Study V72_41 and gave an acceptable protective immune response in comparison with Lot "A" (median age of 15 months). Lot "A" is the current reference standard for the updated potency assay.
- Clinical vaccine was potent at half-dose, based on the fact that a Lot used at half-dose in clinical Study V72P16 was demonstrated to be non-inferior to a full dose. This observation was used to support the proposed release and stability specifications for the updated potency assay.

In addition, it was argued that all lots of vaccine used in clinical trials have been shown to be safe. This claim was used to justify the bacterial endotoxins specification **[information redacted]** and the use of the modified *in vivo* rabbit pyrogen test (RPT).

An interim Company Study Report (CSR) for study V72P16, dated 31 May 2011 was submitted to the TGA and evaluated in the first round Clinical Evaluation Report (see section 8.8 above). It included data collected one month after the primary vaccination series but not data for the booster or 12 month immunogenicity (secondary objectives). In the CER (above) the study was evaluated in the context of rates of fever and the ability of paracetamol to reduce the rate of fever without adversely affecting the immune response in vaccinees. A CSR for study V72_41 was not submitted to the TGA as part of the original application and was belatedly submitted at the request of the TGA. The purpose of this supplementary evaluation is to review the design, conduct and results of studies V72P16 and V72_41 to confirm the veracity of the sponsor's claims.

12.2. Study V72P16

12.2.1. Design and conduct

Study V72P16 was a partially observer-blind, randomised, controlled multicentre dose-ranging and formulation-finding study conducted in Europe and South America in 2-month-old infants born after full term pregnancy with an estimated gestational age ≥ 37 weeks and a birth weight ≥ 2.5 kg.

The goal of the study was to investigate whether different formulations of rMenB+OMV NZ or rMenB alone (no OMV) vaccine induced sufficient immune response when given to healthy infants at 2, 3 and 4 months of age, as measured by the percentage of subjects with serum bactericidal assay with human serum as the source of exogenous complement (hSBA) titre ≥1:5, at 1 month after the third vaccination. The formulations included OMV ½ or ¼ dose; recombinant proteins and OMV both ½ dose; and formulations manufactured using different processes in the Phase 2 and Phase 3 studies. Subjects in all vaccination groups concomitantly received routine vaccines.

The study also assessed the effect of the various formulations and dose strengths on the frequency of post-vaccination febrile reactions and whether prophylactic administration of paracetamol decreased the incidence of febrile reactions following vaccination without impacting the immunogenicity of rMenB OMV NZ and the routine infant vaccines.

A Lot was used for the immunisation of a full-dose rMenB+OMV NZ group [B+OMV]; a group that received half dose of both the recombinant proteins and OMV [1/2(B+OMV)]; and subjects who also received concomitant paracetamol for fever prophylaxis [Par+B+OMV]. Although data for the Par+B+OMV group are not central to the issue at hand, results for this group are shown in this review for completeness and to supplement the discussion in the CER at section 8.8,

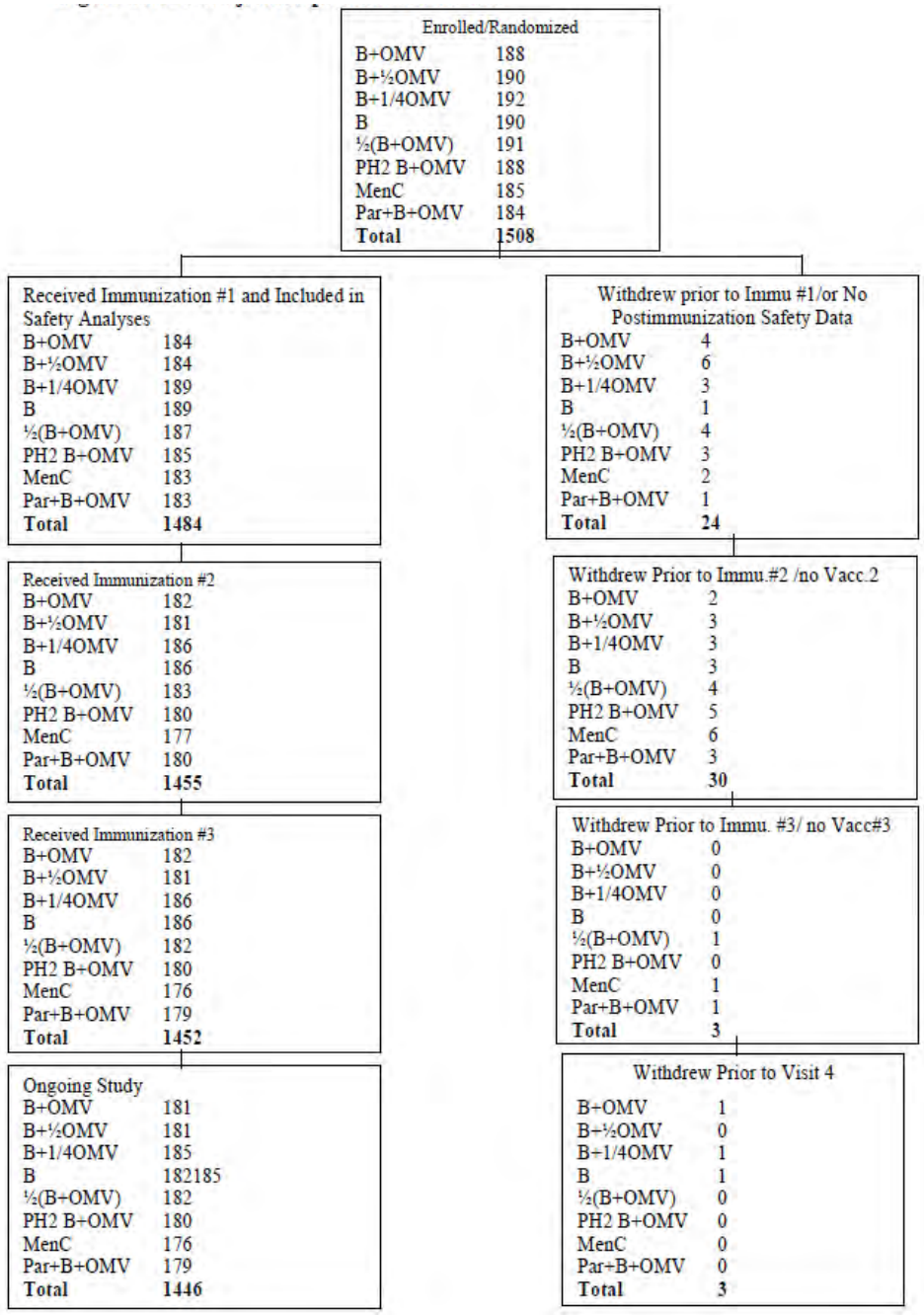
above. A Lot was used at a median age of 27 months, with an age of the lot at first injection of 20 months and an age of the lot at last injection of 34 months.

The primary immunogenicity endpoint was the percentage of subjects with hSBA ≥1:5 to *N. meningitidis* serogroup B reference strains 44/76, 5/99 and NZ98/254 at one month after the third vaccine dose. Secondary immunogenicity endpoints of particular relevance to this review were hSBA geometric mean titres (GMTs) for the reference strains at one month after third vaccination; and geometric mean ratio (GMR) of one month post third vaccination GMTs over baseline. A per protocol (PP) analysis was conducted as the hSBA modified intention-to-treat (MITT) and PP populations did not differ by >10%.

12.2.2. Results

A total of 1508 infants were enrolled and randomised to one of 8 vaccination groups as shown in Figure 16. The baseline demographic data were comparable for all treatment groups. The number of subjects who received a three-dose primary vaccination using a Lot at 2, 3 and 4 months of age was 182 in the full dose group; 184 in the half dose group; and 179 in the group that also received prophylactic paracetamol.

Figure 16: Study V72P16 – Disposition of study subjects



12.2.2.1. Proportion of subjects achieving titres ≥ 1:5 at 1 month after completion of vaccination

Table 64 summarises the proportion of subjects with titres ≥ 1:5. At one month post vaccination, 99% to 100% of subjects achieved bactericidal titres ≥1:5 against reference strains 44/76 and 5/99 for the full-dose group as well as for the half-dose group. At the same time point, 78% (95%CI: 71 – 84%) of the subjects in the full-dose group achieved hSBA ≥ 1:5 for strain NZ98/254, compared to 62% (95%CI: 55 – 69%) of the subjects receiving the half-dose of vaccine from a Lot.

The sponsor also provided a comparison of the results from this study with those for subjects from Study V72P12 who were immunised with a Bexsero Lot at 2, 3 and 4 months of age. These subjects also received concomitant routine vaccinations. The median age of a Lot was 16 months, with an age of the lot at first injection of 9 months and an age of the lot at last injection

of 23 months. Table 64 shows the results observed for the full dose group in Study V72P16 were consistent with those observed for subjects in the corresponding group in Study V72P12.

Table 64. % subjects with hSBA≥ 1:5 following a 3-dose schedule of Bexsero in infants at 2, 3 & 4 months of age – PP population

	Study V72P16			Study V72P12
Lot Median age (months) of lot at injection [first - last injection]	**Lot No. 27 [20 – 34]**			**Lot No. 16 [9 – 23]**
	Full dose	**Half dose**	**Full dose + paracetamol**	**Full dose**
44/76				
Baseline [% (95% CI)]	5%; n=165 (2 – 9%)	4%; n=169 (2 – 8%)	3%; n=163 (1 – 7%)	6%; n=285 (4 – 9%)
1 month after 3rd dose [% (95% CI)]	100%; n=169 (98–100%)	99%; n=168 (97–100%)	100%; n=164 (98 – 100%)	99%; n=273 (97 - 100%)
5/99				
Baseline [% (95% CI)]	5%; n=161 (2 – 10%)	8%; n=166 (5 – 14%)	3%; n=155 (1 – 7%)	4%; n=280 (2 – 7%)
1 month after 3rd dose [% (95% CI)]	99%; n=163 (97–100%)	100%; n=165 (98–100%)	99%; n=157 (97 – 100%)	100%; n=275 (99 – 100%)
NZ98/254				
Baseline [% (95% CI)]	1%; n=169 (0 – 4%)	1%; n=172 (0 – 4%)	1%; n=166 (0.015-3%)	2%; n=283 (1 – 5%)
1 month after 3rd dose [% (95% CI)]	78%; n=133 (71 – 84%)	62%; n=107 (55 – 69%)	75%; n=165 (67 – 81%)	81%; n=274 (76 – 86%)
M10713				
Baseline [% (95% CI)]	37%; n=30 (20 – 56%)			36%; n=112 (27 – 45%)
1 month after 3rd dose [% (95% CI)]	43%; n=35 (26 – 61%)			37%; n=112 (28 – 46%)

12.2.2.2. hSBA GMTs and GMRs against reference strains

hSBA GMTs against the reference strains, GMRs to baseline 1 month following the third vaccination and their respective 95% CIs are shown in Table 65. Significant increases in hSBA GMTs against each of the three reference strains were observed following immunisation with the full and half doses of vaccine from a Lot, although responses with the full-dose vaccine were higher than half dose vaccine. Results for the full dose group were consistent with those observed in Study V72P12.

Table 65. GMTs* and GMRs against reference strains following a 3-dose schedule of Bexsero in infants at 2, 3 & 4 months of age – PP population

	Study V72P16				Study V72P12
Lot Median age (months) of lot at injection [first - last injection]	**Lot No. 27 [20 – 34]**				**Lot No. 16 [9 – 23]**
	Full dose	**Half dose**	**GMR half: full-dose**	**Full dose + Par**	**Full dose**
44/76					
Baseline [% (95% CI)]	1.24; n=165 (1.13 – 1.36)	1.31; n=169 (1.2 – 1.43)		1.18; n=163 (1.08 – 1.3)	1.34; n=285 (1.23 – 1.46)
1 month after 3rd dose [% (95% CI)]	100; n=169 (90 – 112)	72; n=168 (64 – 80)	0.71 (0.61 – 0.83)	101; n=164 (90 – 144)	82; n=273 (75 – 91)
GMR 1 month after 3rd dose to baseline (95% CI)	80; n=156 (69 – 93)	54; n=160 (47 – 63)		83; n=154 (71 – 96)	61; n=262 (53 – 70)

	Study V72P16				Study V72P12
Lot Median age (months) of lot at injection [first - last injection]	**Lot No. 27 [20 – 34]**				**Lot No. 16 [9 – 23]**
	Full dose	**Half dose**	**GMR half: full-dose**	**Full dose + Par**	**Full dose**
5/99					
Baseline [% (95% CI)]	1.17; n=161 (1.07 – 1.29)	1.29; n=166 (1.18 – 1.42)		1.06; n=155 (0.96 – 1.17	1.19; n=280 (1.09 – 1.3)
1 month after 3rd dose [% (95% CI)]	393; n=164 (344 – 448)	318; n=165 (279 –363)	0.8 (0.68 – 0.96)	449; n=157 (392 – 515	325; n=275 (292 – 362)
GMR 1 month after 3rd dose to baseline (95% CI)	345; n=151 (291 – 407)	246; n=153 (208 – 290)		417; n=140 (350 – 497)	271; n=257 (231 – 318)
NZ98/254					
Baseline [% (95% CI)]	1.03; n=169 (1.0 – 1.07)	1.03; n=171 (1.0 – 1.06)		1.02; n=166 (0.99 – 1.05)	1.06; n=283 (1 – 1.12)
1 month after 3rd dose [% (95% CI)]	9.91; n=170 (8.48 – 12)	6.7; n=172 (5.74 – 7.81)	0.67 (0.55 – 0.82)	8.25; n=165 (7.03 – 9.67)	11; n=274 (9.14 – 12)
GMR 1 month after 3rd dose to baseline (95% CI)	9.45; n=161 (8.02 – 11)	6.48; n=165 5.51 – 7.61		8.45; n=157 (7.14 – 9.99)	10; n=258 (8.52 – 12)
Antigen 287-953					
Baseline [% (95% CI)]	21; n=171 (19 – 22)	22; n=172 (20 – 21)		21; n=168 (20 – 22)	22; n=293 (21 – 24)
1 month after 3rd dose [% (95% CI)]	3540; n=172 (3141 – 3990)	2370; n=174 (2105 – 2668)	0.67 (0.57 – 0.78)	3514; n=165 (3106 – 3975)	3254; n=281 (2988 – 3545)
GMC ratio 1 month after 3rd dose to baseline (95% CI)	178; n=164 (156 – 203)	109; n=169 (95 – 124)		166; n=159 (145 – 191)	145; n=275 (128 – 275)

** GMC for ELISA IgG to antigen 287-953

The adequacy of the responses to reduced antigen doses compared to full doses were analysed using a non-inferiority approach whereby a 95% lower confidence limit > 0.5 for the ratio of GMTs was used to conclude non-inferiority. (Note: geometric mean concentrations (GMCs) were used for enzyme linked immunesorbent assay (ELISA) IgG to antigen 287-953). The interval 0.5 to 2.0 has been traditionally used to evaluate consistency of the immune response between vaccine lots. From Table 65 it can be appreciated that the 95%CI for the GMT ratios for half dose: full dose responses for each of the 3 reference strains all fell within the requisite interval. However, also of note, the upper limits of the 95%CIs for all three strains were less than 1.0 (indicating that the GMTs were lower for the reduced doses of antigen). Nevertheless, the sponsor considered these data indicated that an acceptable protective immune response was achieved with the half dose in light of the high percentage of subjects achieving a protective level of bactericidal antibody following vaccination.

Comment: This large, well designed and conducted study demonstrates the potency of the vaccine for at least 24 months. When a full dose of vaccine was administered at a median lot age of 27 months 99-100% subjects achieved hSBA titres ≥ 1:5 against reference strains 44/76 and 5/99 one month post vaccination and >70% achieved hSBA ≥ 1:5 for strain NZ98/254. These results were consistent with the GMT responses and GMR at 1 month post vaccination against each of the 3 reference strains. Also, results for the full dose group were consistent with those observed when the vaccine (median age 16 months) was administered under similar conditions in Study V72P12.

As mentioned under Background, above, Study V72P16 was evaluated in the first round CER in the context of rates of fever and the ability of paracetamol to reduce the rate of fever without adversely affecting the immune response in vaccines. However, this study also served as a dose-finding study. In this regard, it is of note that bactericidal GMTs against each of the 3 reference strains were reduced when the recombinant protein components

were reduced by half. Also, reducing the OMV dose to half resulted in decrease in response rate against NZ98/254 from 78% to 67% (note that another vaccination group a formulation in which full strength recombinant proteins and half strength OMV was given, had a response rate of 67%). However, lowering the dose of OMV did not significantly alter the rate of systemic or local reactions, indicating there would be no safety benefit from a lower dose of OMV whilst immune response could be compromised. Thus, the results of this study also serve to further underline the dose chosen for the commercial formulation.

12.3. Study V72_41

12.3.1. Design and conduct

Study V72_41 was a phase III observer-blind, randomised, controlled multicentre study conducted in Australia (5 active centres) and Canada (7 active centres) that evaluated the safety and immunogenicity of rMenB+OMV NZ vaccine manufactured at 2 different sites, in healthy adolescents aged 11-17 years.

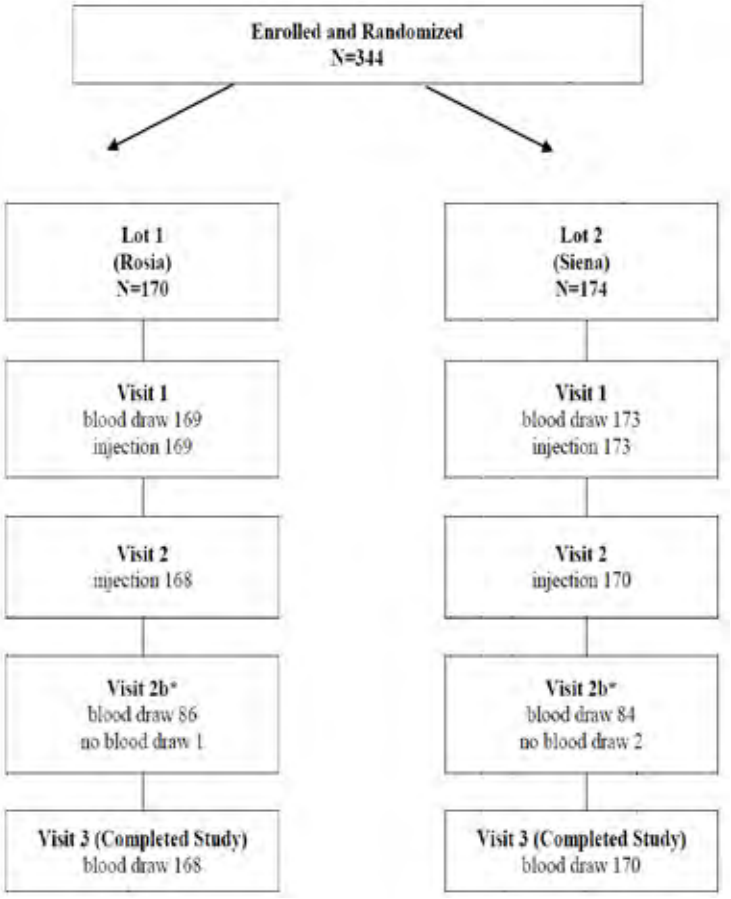
The primary aim of the study was to demonstrate the equivalence of 2 lots of rMenB + OMV NZ as measured by hSBA GMTs against the reference strains 44/76, 5/99, and NZ98/254 and as measured by ELISA GMCs against vaccine antigen 287-953, approximately 30 days after a primary vaccination course of two doses administered one month apart. A Lot had a median age of 29 months, with an age of 28 months at first injection and 30 months at the time of the last injection. In comparison, the other Lot had a median age of 16 months, with an age of 14 months at first injection and 16 months at the time of the last injection.

The 2 lots were considered to be equivalent with respect to immune response if, at one month following the second vaccination, the two-sided 95% confidence interval (CI) of the ratio of the hSBA GMTs for each of 3 reference strains and the two-sided 95% CI of the ratio of the ELISA GMCs against vaccine antigen 287-953 were contained within the interval 0.5 to 2.0. Other immunogenicity endpoints included the percentage of subjects in each lot with hSBA ≥1:5 at one month after the second vaccination for each of the three reference strains.

12.3.2. Results

Overall, 344 subjects were enrolled in the study and the disposition of these subjects is shown in Figure 17.

Figure 17. Study V72_41 – Disposition of study subjects



A total of 170 were randomised to receive Lot 1 and 174 were randomised to receive Lot 2. The demographic and other baseline characteristics of the two groups were well matched, except for the gender differences. In both groups there was a higher proportion of males than females and there was a 5% higher percentage of males in the group that received Lot 1 than received Lot 2 (58% vs. 53%). The MITT population differed from the per protocol (PP) population by 12%, but the immunogenicity results in the PP immunogenicity population and MITT population were similar for the primary endpoint. The PP immunogenicity population comprised 299 subjects - 147 subjects from Lot 1 and 152 subjects from Lot 2 - and forms the basis of the results presented below.

12.3.2.1. hSBA GMTs and GMRs against reference strains

hSBA GMTs against the reference strains, GMRs to baseline 1 month following the second vaccination and their respective 95% CIs are shown in Table 66 Significant increases in hSBA GMTs against reference strains 44/76, 5/99 and NZ98/254 and against vaccine antigen 287-953 were observed 1 month after completion of immunisation. The 95%CIs for the ratios of GMTs for the 2 lots fell within the equivalence interval of 0.5 to 2.0.

Table 66. GMTs and GMRs against reference strains following a 2-dose 0, 1 month schedule in subjects aged 11-17 years – PP population

	Study V72_41			Study V72P10 (subjects with baseline hSBA <1:4)	
Lot	**1**	**2**	**Lot 1: Lot 2**	**X38D27N1**	
				rMenB01	**rMenB012**
44/76					
Baseline GMT (95% CI)	1.07 (1.1 – 1.14) N=147	1.03 (0.97 – 1.1) N=152	1.04 (0.95 – 1.13)	1.12 (1.07 – 1.17) N=210	1.13 (1.08 – 1.19) N=180
GMT 1 month after 2nd dose (95% CI)	111 (96 – 129) N=147	111 (96 – 128) N=151	1.0 (0.82 – 1.23)	135 (112 – 162) N=202	132 (108 – 161) N=167
GMR 1 month after 2nd dose to baseline (95% CI)	104 (89 – 121) N=147	107 (92 – 124) N=151	0.97 (0.79 – 1.19)	102 (100 – 144) N=202	115 (94 – 140) N=167
5/99					
Baseline GMT (95% CI)	1.17 (1.04–1.31) N=147	1.19 (1.06 – 1.33) N=152	0.98 (0.84 – 1.15)	1.15 (1.1 – 1.2) N=240	1.15 (1.09 – 1.2) N=216
GMT 1 month after 2nd dose (95% CI)	183 (160 – 209) N=147	199 (174 – 227) N=152	0.92 (0.77 – 1.11)	402 (343 – 472) N=230	416 (350 – 493) N=197
GMR 1 month after 2nd dose to baseline (95% CI)	156 (133 – 183) N=147	167 (143 – 195) N=152	0.93 (0.75 – 1.16)	352 (299-414) N=229	365 (306 – 435) N=197
NZ98/254					
Baseline GMT (95% CI)	1.07 (1.1 – 1.15) N=147	1.04 (0.97 – 1.11) N=152	1.04 (0.94 – 1.14)	1.11 (1.06 – 1.16) N=227	1.11 (1.06 – 1.16) N=224
GMT 1 month after 2nd dose (95% CI)	9.27 (7.44 – 12) N=147	11 (9.22 – 14) N=151	0.81 (0.6 – 1.09)	56 (46-67) N=219	59 (49 – 72) N=208
GMR 1 month after 2nd dose to baseline (95% CI)	8.63 (6.99 – 11) N=147	11 (8.99 – 14) N=151	0.78 (0.59 – 1.04)	50 (41 – 60) N=218	53 (44 – 64) N=208
Antigen 287-953					
Baseline ELISA GMC (95% CI)	24 (22 – 26) N=147	21 (20 – 23) N=152	1.11 (0.99 – 1.25)	NM	NM
ELISA GMC 1 month after 2nd dose (95% CI)	2729 (2338–3186) N=147	3291 (2829-3828) N=152	0.83 (0.67 – 1.02)	NM	NM
GMR 1 month after 2nd dose to baseline (95% CI)	115 (96 – 137) N=147	154 (130 – 183) N=152	0.75 (0.59 – 0.94)	NM	NM

NM: ELISA IgG to antigen 287-953 was not measured in Study V72P10

12.3.2.2. Proportion of subjects achieving titres ≥ 1:5 at 1 month after completion of vaccination

Table 67 summarises the proportion of subjects with titres ≥ 1:5. At one month post vaccination, 99% to 100% of subjects achieved bactericidal titres ≥1:5 against reference strains 44/76 and 5/99 for both lots. At the same time point, 70% (95%CI: 62 – 77%) of the subjects who received Lot 1 achieved hSBA ≥ 1:5 for strain NZ98/254, compared to 79% (95%CI: 72 – 86%) of the subjects who received Lot 2.

Table 67. % subjects with hSBA ≥1:4, 1:5 or 1:8) at 1 month after a 2-dose 0, 1 month schedule in adolescents aged 11-17 years - PP population

	Study V72_41		Study V72P10	
Lot	**1**	**2**	**X38D27N1 rMenB01 + rMenB012; all subjects**	
Age of lot (months)			Not reported	
Median [age at 1st injection - age at last injection]	15 [14 – 16]	29 [28 – 30]		
hSBA threshold	≥1:5	≥1:5	≥1:4	≥1:8
44/76				
Baseline [% (95% CI)]	2%; n=147 (0 – 6%)	2%; n=152 (0 – 6%)	43%; n=679 (39 – 46%)	32%; n=679 (29 – 36%)
1 month after vaccination completed [% (95% CI)]	99%; n=147 (96–100%)	99%; n=152 (96–100%)	100%; n=638 (99 – 100%)	99%; n=638 (98 - 100%)
5/99				
Baseline [% (95% CI)]	6%; n=147 (3 – 11%)	7%; n=152 (4 – 13%)	33%; n=679 (29 – 37%)	22%; n=639 (19 – 25%)
1 month after vaccination completed [% (95% CI)]	100%; n=147 (98–100%)	100%; n=152 (98–100%)	100%; n=639 (99 – 100%)	100%; n=639 (99 – 100%)
NZ98/254				
Baseline [% (95% CI)]	3%; n=147 (1 – 7%)	1%; n=152 (0.02 – 4%)	33%; n=678 (30 – 37%)	25%; n=639 (22 – 29%)
1 month after vaccination completed [% (95% CI)]	70%; n=147 (62 – 77%)	79%; n=152 (72 – 86%)	100%; n=639 (99 – 100%)	99%; n=639 (98 – 99%)

Comment: The comparability of immune response to the 2 Bexsero lots (with respective median ages of 16 and 29 months) was demonstrated on the basis that the ratios of GMTs for the 2 lots fell within the requisite equivalence interval of 0.5 to 2.0 for all reference strains. In contrast to the data presented for study V72P16 for infants, no comparisons with data from other studies in adolescents were presented by the sponsor. This evaluator has included data from the only other adolescent study - V72P10 - in Tables 66 and 67 to give some context to the results observed in Study V72_41. In Study V72P10 Bexsero was administered in an identical fashion to that in Study V72_41 for 2 subgroups of patients - those who received 2 doses at 0, 1 months (so-called rMenB01 group) and those who received doses at 0, 1 months as part of a 3 dose schedule and who had data 1 month post injection 2 and prior to the third dose (so-called rMenB012 group). Data from these subgroups were available in the CSR for Study V72P10 and have been used to compile Tables 66 and 67. When reviewing the results from Study V72P10 it is important to note the following:

- approximately 30% to 40% subjects across the vaccine groups had baseline hSBA titres ≥1:4 against the reference strains. Thus, a more meaningful comparison for the proportion of subjects who achieved titres ≥ 1:4 at 1 month post vaccination should be for subjects who had a titre <1:4 at baseline. However, all subjects in the rMenB01 and rMenB012 groups achieved titres ≥ 1:4 against each reference strain at 1 month post vaccination (see Table 67), so the point estimates for the group with titres <1:4 at baseline would also be 100%, although the 95%CIs would be wider on account of the smaller sample sizes;
- one would expect that the GMTs at baseline would differ for those subjects with titres above and below 1:4, so the GMT and GMR results are presented for subjects with titres <1:4 at baseline in Table 66;
- Study V72P10 used a threshold for hSBA at 1 month post vaccination of 1:4, whereas the threshold used in Study V72_41 was more conservative at 1:5. However, data for an even more conservative threshold of 1:8 were also available for Study V72P10 and the results for a threshold of 1:5 should be at least the same as that for the threshold of

1:8. The results for hSBA ≥ 1:8 ranged from 99 to 100% across the 3 reference strains when all subjects were considered. Although these data were not stratified according to titres < or ≥ 1:4 at baseline, given the actual results, it can be reasonably expected that the point estimates for the proportion of subjects with titres <1:4 at baseline who achieved hSBA ≥ 1:8 would be very close to 99 to 100%; and

- the age of the lot used in Study V72P10 was not stated.

It is against this background that the following observations are made:

- GMT and GMR responses against 44/76 were consistent between the two studies and across all lots (Table 66);
- GMT and GMR responses against 5/99 and N98/254 were much lower in Study V72_41 than Study V72P10 but the responses in Study V72_41 still appear to be at an acceptable level (Table 66); and
- The immune response as measured by the proportion of subjects with hSBA ≥ 1:5 against NZ98/254 at 1 month after the second dose was much lower for both lots used in Study V72_41 (Table 67). Of particular note, the lower bound of the 95%CI for the proportion of subjects achieving a titre ≥ 1:5 with Lot 1 was only 62% (below 70% - the threshold used in the pivotal study V72P13 to determine if the immune response was adequate). Lot 1 was used at an age well within the proposed shelf life for the product, whereas Lot 2 (which had a 95%CI LL of 72%) was beyond the proposed shelf life. This is further reflected in Table 68 below, which presents the proportion of subjects with a 4-fold increase in hSBA titre from baseline for each antigen. In this table the results presented for Study V72_41 were derived by this Delegate from IPD listings within Appendix 16.2.6.1 of the CSR. It can be appreciated that the lowest response against NZ98/254 was observed for Lot 1. No attempt was made by this Delegate to calculate 95% CIs for these estimates but it is anticipated that the lower bound of the 95%CI for the response against NZ98/254 would be <70%.

Table 68. % subjects with 4-fold increase in hSBA from baseline at 1 month after a 2-dose 0, 1 month schedule in adolescents aged 11-17 years – PP population

	Study V72_41		Study V72P10 (subjects with baseline hSBA <1:4)	
Lot	**101601**	**090101**	**X38D27N1**	
			rMenB01	rMenB012
44/76	99% N=147	99% N=152	100% (98 – 100%) N=202	99% (97 – 100%) N=167
5/99	100% N=147	99% N=152	100% (98 – 100%) N=229	98% (96 – 100%) N=197
NZ98/254	74% N=147	85% N=152	99% (97 – 100%) N=281	99% (97 – 100%) N=208
Antigen 287-953	100% N=147	100% N=152	NM	NM

NM not measured in this study

12.4. Safety considerations

One concern raised by the Quality evaluator in the context of the stability of Bexsero was whether the adsorption of endotoxin to aluminium hydroxide might decrease during storage, leading to an increase in available endotoxin (and LPS). If such an outcome were to occur, it could be expected that there would be an increase in adverse events indicative of reactogenicity.

Adverse events (local, systemic and other reactions) indicative of reactogenicity and occurring within 6 days after the day of injection were solicited in all the clinical studies of Bexsero, which allows assessment of whether trends were evident for an increase in these events when older lots of vaccine were used. Local reactions of interest in infants and adolescents were tenderness/pain, erythema, swelling and induration. Systemic reactions in infants were change in eating habits, sleepiness, unusual crying, vomiting, diarrhoea, irritability and rash whilst, for adolescents, solicited systemic events were malaise, myalgia, arthralgia, headache and nausea. Other indicators of reactogenicity common to both age groups were fever and use of analgesic/antipyretics.

Table 69 compares the indicators of reactogenicity observed in infants in Studies V72P16 (median lot age 27 months) and V72P12 (median lot age 16 months).

Table 69. Reactogenicity of Bexsero in infants day 1 to 7 post injection – median lot age 27 months (Study V72P16) vs. 16 months (Study V72P12)

			Study V72P16		Study V72P12
			B + OMV n=184	Par+B+OMV n=183	B + OMV n=318
Local reactogenicity	*Tenderness*	1st inj	61%	34%	66%
		2nd inj	66%	47%	63%
		3rd inj	55%	37%	56%
	Erythema	1st inj	59%	40%	65%
		2nd inj	57%	52%	70%
		3rd inj	60%	51%	66%
	Induration	1st inj	55%	45%	47%
		2nd inj	57%	44%	54%
		3rd inj	53%	45%	54%
	Swelling	1st inj	31%	22%	26%
		2nd inj	35%	29%	31%
		3rd inj	30%	26%	31%
Systemic reactogenicity	*Change in eating habits*	1st inj	41%	36%	59%
		2nd inj	34%	30%	56%
		3rd inj	26%	27%	44%
	Sleepiness	1st inj	65%	63%	73%
		2nd inj	58%	47%	69%
		3rd inj	41%	42%	55%
	Vomiting	1st inj	14%	12%	14%
		2nd inj	10%	11%	17%
		3rd inj	4%	11%	15%
	Diarrhoea	1st inj	32%	22%	25%
		2nd inj	24%	22%	27%
		3rd inj	18%	18%	15%
	Irritability	1st inj	70%	53%	79%
		2nd inj	71%	55%	75%
		3rd inj	63%	47%	66%
	Unusual crying	1st inj	52%	40%	68%
		2nd inj	49%	39%	65%
		3rd inj	41%	26%	61%
	Rash	1st inj	3%	3%	6%
		2nd inj	2%	3%	4%
		3rd inj	1%	3%	5%
	Urticarial rash	1st inj	1%	2%	1%
		2nd inj	2%	0%	<1%
		3rd inj	1%	2%	1%
	Fever (≥ 38.0°C)	1st inj	51%	25%	58%
		2nd inj	49%	19%	59%
		3rd inj	30%	11%	44%

It can be appreciated similar results were obtained in the 2 studies across the spectrum of specified local and systemic events. Also there was no evidence of a trend toward increasing events with the second of third injections for either vaccine lot.

It is also of note that there were no reports of anaphylaxis, bronchospasm, wheeze, hypersensitivity or other events suggestive of severe allergic reactions in Study V72P16. There were 2 reports each of wheezing and bronchospasm occurring in the corresponding treatment group in Study V72P12. There were 3 reports of febrile convulsion in V72P16. It was not possible to tell from the CSR which treatment group these cases belonged to but in all cases they occurred more than 120 days post completion of the vaccination course, indicating there was no temporal link between vaccination and the seizures. In study V72P12, there was one report of convulsion occurring secondary to a glioma.

The within-study comparison of Lot 1 vs. Lot 2 administered to adolescents in Study V72_41 and the indirect comparison of results from studies V72_41 and V72P10, yielded similar reactogenicity profiles, as shown in Table 70.

Table 70. Reactogenicity of Bexsero in adolescents, day 1 to 7 post injection – Study V72_41 (median lot age 29 and 15 months) vs. Study V72P10

			Study V72_41		Study V72P10	
			Lot 1 Median lot age 15 months n=169	Lot 2 Median lot age 29 months n=173	Lot age not stated	
					rMenB01 n=375	rMenB012 n=373
Local reactogenicity	*Pain*	1st inj	94%	97%	93%	89%
		2nd inj	89%	93%	86%	87%
	Erythema	1st inj	48%	43%	52%	56%
		2nd inj	55%	52%	52%	53%
	Induration	1st inj	24%	29%	44%	44%
		2nd inj	28%	27%	39%	45%
	Swelling	1st inj	30%	25%	39%	42%
		2nd inj	35%	34%	40%	39%
Systemic reactogenicity	*Arthralgia*	1st inj	12%	17%	23%	27%
		2nd inj	9%	16%	21%	22%
	Fatigue/ Malaise	1st inj	36%	35%	55%	55%
		2nd inj	29%	36%	49%	54%
	Headache	1st inj	32%	36%	50%	46%
		2nd inj	28%	39%	43%	45%
	Myalgia	1st inj	53%	59%	47%	44%
		2nd inj	37%	41%	39%	41%
	Nausea	1st inj	18%	19%	19%	20%
		2nd inj	18%	21%	15%	18%
	Rash	1st inj	4%	4%	NA	NA
		2nd inj	4%	6%	NA	NA
	Fever (≥ 38.5°C)	1st inj	3%	2%	2%	3%
		2nd inj	2%	1%	5%	3%

NA - not applicable. Rash was not included as an indicator of systemic reactogenicity in this study

Further to the solicited adverse events, there were no reports of urticaria or hypersensitivity occurring within 7 days of any vaccination in either study, although there was 1 report of asthma occurring after injection 1 and injection 2 with Lot 2 in Study V72_41. In Study V72_41 there was also a single report of urticaria (considered unrelated to vaccination) occurring more than 8 days after the second immunisation with Lot 1.

> **Comment**: Although the safety profiles of aged lots appear similar to younger lots, the only direct comparison of aged and younger lots occurred in Study V72_41. Also, the overall datasets for a full dose of the aged lots was very limited (367 infants and 173 adolescents). This limits the conclusions that can be drawn regarding the frequency of serious events such as anaphylaxis, hypersensitivity reactions and febrile convulsions.

12.5. Conclusions

Vaccine from an older lot (median age 27 months) when administered as a full dose to infants was found to result in an acceptable immune response as measured by the proportions of subjects with hSBA titres ≥ 1:5 against each of the 3 reference strains 44/76, 5/99 and NZ98/254 at 1 month post vaccination, and GMTs and GMRs at the same time point. The results were also consistent with those observed when vaccine from a lot with median age 16 months was administered under similar conditions in Study V72P12.

Administration of a full dose of an older lot (median age 29 months) to adolescents in Study V72_41 gave a comparable immune response to that of a younger lot (median age 15 months) as indicated by ratios of GMTs for the 2 lots falling within the requisite equivalence interval of 0.5 to 2.0 for each of the 3 reference strains. The GMT and GMR responses for the older lot against the reference strains were also comparable to that of the younger lot. Whilst the overall results for the older lot were consistent with an acceptable immune response, some aspects of the immunogenicity of the younger lot (Lot 1) are of concern. In particular, the lower bound of the 95%CI for the proportion of subjects achieving a titre ≥ 1:5 against reference strain NZ98/254 with Lot 1 was only 62% (below the 70% threshold considered to be an acceptable immune response in the pivotal study in infants) and the proportion of subjects with a 4-fold increase in hSBA titre from baseline against NZ98/254 was 74% compared to 85% for the older lot. Lot 1 was chosen as the reference standard for the modified potency assay and study V72_41 was the first clinical study in which it had been used. It is also of note that the results achieved with respect to immunogenicity against reference strain with NZ98/254 in study V72_41 were much lower than observed in the only other study involving adolescents (V72P10), even when the much higher prevalence of functional antibodies at baseline in that study was discounted. The higher baseline titres might be explained by the fact that study V72P10 was conducted in Chile where subjects may have been more likely to have had prior exposure to colonizing bacteria with antigens that cross-reacted with those of the serogroup B test strains.

Overall, the clinical data appears generally supportive of the sponsor's claim that lots used beyond the proposed 24 month shelf life gave acceptable protective immune response. No particular safety issues were evident from the use of aged lots. However, the actual data are quite limited. The sponsor should comment specifically on the immunogenicity results obtained for Lot 1 in this study and the implications of this for its use as the reference standard for the modified potency assay.[26]

[26] This was addressed in the sponsor's response to the Delegate's Overview. See AusPAR section on *Overall conclusion and risk/benefit assessment Response from Sponsor*.

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