

CLINICAL STUDY PROTOCOL V59_75 Version # 1

A Phase IV, Open-Label, Multi-Center Study to Evaluate the Safety and the 1-year Persistence of Antibody Response Among Children Who Received 4 Doses of the Novartis MenACWY Conjugate Vaccine at 2, 4, 6 and 12 Months of Age in South Korea

Evaluation of Antibody persistence following 4 MenACWY vaccinations

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PROTOCOL SYNOPSIS V59_75 VERSION 1

Name of Sponsor: Novartis Pharma Services AG	Protocol number: V59_75	Generic name of study vaccine(s): MenACWY-CRM (Menveo [®]) is a Meningococcal (Groups A, C, Y and W-135), Oligosaccharide Diphtheria CRM ₁₉₇ Conjugate Vaccine.
Title of Study: A Phase IV, Open-Label, Multi-center study to evaluate the Safety and the 1-year persistence of antibody response among children who received 4 doses of the Novartis MenACWY Conjugate Vaccine at 2, 4, 6 and 12 months of age in South Korea.		
Study Period: The duration of study participation for each subject is approximately 22 months.		Clinical Phase: Phase IV
Background and Rationale: The purpose/aim of this study is to evaluate the persistence of the antibody response in children approximately 24 months of age who receive 4 doses of Menveo [®] at 2, 4, 6, 12 months of age. <i>Neisseria meningitidis</i> is a leading cause of bacterial meningitis and sepsis worldwide, (Rouphael and Stephens 2012, Al-Tawfiq et al 2010, Hill et al 2010, Deasy and Read 2011) capable of causing outbreaks and epidemics of invasive disease. Meningococcal disease causes high rates of morbidity and mortality even among patients who receive early antibiotic treatment. Based on antigenic differences in their capsular polysaccharide, 13 serogroups of <i>N. meningitidis</i> have been identified. Virtually all disease-associated isolates are encapsulated, with serogroups A, B, C, W and Y being responsible for the large majority of invasive meningococcal infections worldwide. Novartis developed a quadrivalent meningococcal vaccine against serogroups A, C, W and Y (MenACWY-CRM, Menveo [®]) which is licensed in more than 60 countries. Recently this vaccine was approved for use in infants as young as 2 months of age in the US, Argentina, South Korea and other countries. MenACWY-CRM is given to infants as a 4-dose series at 2, 4, 6, and 12 months of age; children 7 to 23 months of age should receive a 2-dose series, with the second dose administered in the second year of life. Previous studies have shown that MenACWY-CRM is immunogenic and well tolerated		

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<p>when administered at 2, 4, 6 and 12-13 months of age, or when administered to toddlers as 1 or 2 doses in the second year of life. Limited data are available about long-term persistence of bactericidal antibodies following a 4-dose vaccination series in infants.</p> <p>Novartis MenACWY (Menveo[®] has been approved for use in people 2 months through 55 years of age in the United State and in people 2 years up to 55 in Europe and other countries, including the Republic of South Korea. In South Korea, the indication was extended in May 2014 to infants 2 months of age up to 55, however, the Ministry of Food and Drug Safety (MFDS) of the Republic of South Korea have requested data on immunogenicity persistence in the Korean children who received 4 doses of Menveo[®] at 2, 4, 6, and 12 months of age.</p>		
<p>Study Objectives:</p> <p>Primary Objective(s):</p> <ol style="list-style-type: none"> 1. To evaluate the persistence of the antibody response against <i>N. meningitidis</i> serogroups A, C, W and Y at approximately 1 year after completion of a 4-dose infant vaccination series (2, 4, 6 and 12 months of age) of MenACWY vaccine as measured by hSBA titers ≥ 8. 2. To evaluate the persistence of the antibody response against <i>N. meningitidis</i> serogroups A, C, W and Y at approximately 1 year after completion of a 4-dose infant vaccination series (2, 4, 6 and 12 months of age) of MenACWY vaccine as measured by rSBA titers ≥ 8 and ≥ 128. <p>Secondary Objective(s):</p> <ol style="list-style-type: none"> 1. To describe hSBA titers ≥ 8 and hSBA GMTs against <i>N. meningitidis</i> serogroups A, C, W and Y 1 month after a full vaccination series at 2,4,6 and 12 months of age. 2. To describe rSBA titers ≥ 8 and ≥ 128 and rSBA GMTs against <i>N. meningitidis</i> serogroups A, C, W and Y 1 month after a full vaccination series at 2,4,6 and 12 months of age. 3. To evaluate the persistence of the antibody response against <i>N. meningitidis</i> serogroups A, C, W and Y at approximately 1 year after completion of a 4-dose 		

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<p>infant vaccination series (2, 4, 6 and 12 months of age) of MenACWY vaccine as measured by hSBA GMTs and rSBA GMTs.</p> <p>Safety Objective(s)</p> <p>To assess the safety and tolerability of MenACWY administered at 2-4-6 and 12 months of age.</p>																									
<p>Study Design:</p> <p>This is Phase IV, Open label, Multicenter study. Subject's parents and/or legal guardian will be provided information about the trial. If interested and if eligible, they will then be asked to provide signed informed consent. The initial study visit can occur immediately after signed informed consent has been obtained. Approximately 135 subjects will be enrolled to receive 4 doses of intramuscular MenACWY vaccine at 2, 4, 6 and 12 months of age.</p> <p>A total of two blood samples (up to approx. 5 mL per draw) will be obtained at 13 and 24 months of age.</p> <p>Table 1: Overview of the Study design</p> <table border="1"> <tr> <th>No Subjects</th> <th>Visit 1</th> <th>Visit 2</th> <th>Visit 3</th> <th>Visit 4</th> <th>Visit 5</th> <th>Visit 6</th> </tr> <tr> <td></td> <td>2-Months</td> <td>4-Months</td> <td>6-Months</td> <td>12-Months</td> <td>13- Months</td> <td>24- Months</td> </tr> <tr> <td>135</td> <td>Menveo[®]</td> <td>Menveo[®]</td> <td>Menveo[®]</td> <td>Menveo[®]</td> <td>Blood draw</td> <td>Blood draw</td> </tr> </table> <p>Table 2: Safety Assessment</p> <table border="1"> <tr> <td> <p>Medical history:</p> <p>Any significant past (see details in Section 4.2 and 6.2 of the protocol)</p> </td> <td>From birth</td> </tr> </table>			No Subjects	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6		2-Months	4-Months	6-Months	12-Months	13- Months	24- Months	135	Menveo [®]	Menveo [®]	Menveo [®]	Menveo [®]	Blood draw	Blood draw	<p>Medical history:</p> <p>Any significant past (see details in Section 4.2 and 6.2 of the protocol)</p>	From birth
No Subjects	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6																			
	2-Months	4-Months	6-Months	12-Months	13- Months	24- Months																			
135	Menveo [®]	Menveo [®]	Menveo [®]	Menveo [®]	Blood draw	Blood draw																			
<p>Medical history:</p> <p>Any significant past (see details in Section 4.2 and 6.2 of the protocol)</p>	From birth																								

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Vaccination history: Will be checked to determine subject's eligibility criteria.		From birth
Immediate reactions: Subjects will be assessed for immediate reactions		For 30 minutes after each Men ACWY vaccination
Body Temperature: Body Temperature (tympanic is recommended, but axillary, rectal route is allowed if temperature cannot be taken by tympanic route) and antipyretic/analgesic use will be recorded.		From Day 1 to Day 7 after each Men ACWY vaccination
Solicited local adverse events: Injection site erythema, injection site induration, injection site tenderness.		From Day 1 to Day 7 after each Men ACWY vaccination
Solicited systemic adverse events: Change in eating habits, sleepiness, irritability, vomiting, diarrhea, fever.		From Day 1 to Day 7 after each Men ACWY vaccination
Unsolicited Adverse Events: All medically-attended unsolicited AEs and AEs leading to premature withdrawal will be collected verbally during all clinical visits		From Day 1 of the study to Visit 6 (24 months of age)
Serious AEs (SAEs): All SAEs will be monitored until resolution and/or the cause is identified (<i>if a SAE remains unresolved at study termination, a clinical assessment will be made by the investigator and the Novartis medical monitor to determine whether continued follow up of the SAE is warranted</i>).		From Day 1 of the study to Visit 6 (24 months of age)
Medications: Medications used to treat any medically-attended AE, AEs leading to premature withdrawal and SAE, verbally during all clinical visits		From Day 1 of the study to Visit 6 (24 months of age)

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Number of Subjects planned: Approximately 135 subjects will be enrolled in this study.		
Study Population and Subject Characteristics: The list of inclusion and exclusion criteria is included in protocol section 4.0, Selection of Study Population .		
Study Procedures: <p><u>Visit 1 (Age 2 months) (Day 1).</u> Informed consent must be obtained from the subject's parent(s) or legally acceptable representative(s) prior to the performance of any study related procedures. After receiving the 1st vaccination, subjects will be observed for at least 30 minutes for any immediate reactions. The subjects' parents/legal guardian will be instructed to complete a subject diary daily, reporting solicited local and systemic adverse events (AEs) occurring from Day 1 to Day 7 after vaccination with MenACWY.</p> <p>At Day 3 after vaccination a telephone call will be made to remind the subjects' parents/legal guardian to complete the subject diary .</p> <p><u>Visit 2 (Age 4 Months) (60 days after Visit 1 +/- 7 days).</u> The subject diary will be collected and reviewed with all subject's parents/legal guardian. After receiving the 2nd vaccination, subjects will be observed for at least 30 minutes for any immediate reactions. The subjects' parents/legal guardian will be instructed to complete a subject diary daily, reporting solicited local and systemic adverse events (AEs) occurring from Day 1 to Day 7 after vaccination with MenACWY.</p> <p>At Day 3 after vaccination a telephone call will be made to remind the subjects' parents/legal guardian to complete the subject diary.</p> <p><u>Visit 3 (Age 6 months) (60 days after Visit 2 +/- 7 days).</u> The subject diary will be collected and reviewed with all subject's parents/legal guardian. After receiving the 3rd vaccination, subjects will be observed for at least 30 minutes for any immediate reactions. The subjects' parents/legal guardian will be instructed to complete a subject diary daily, reporting solicited local and systemic adverse events (AEs) occurring from</p>		

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<p>Day 1 to Day 7 after vaccination with MenACWY.</p> <p>At Day 3 after vaccination a telephone call will be made to remind the subjects' parents/legal guardian to complete the subject diary.</p> <p><u>Visit 4 (Age 12 Months) (Inclusive + 14 days).</u> The subject diary will be collected and reviewed with all subject's parents/legal guardian.</p> <p>After receiving 4th vaccination, subjects will be observed for at least 30 minutes for any immediate reactions. The subjects' parents/legal guardian will be instructed to complete a subject diary daily, reporting solicited local and systemic adverse events (AEs) occurring from Day 1 to Day 7 after vaccination with MenACWY.</p> <p>At Day 3 after vaccination a telephone call will be made to remind the subjects' parents/legal guardian to complete the subject diary.</p> <p><u>Visit 5 (Age 13 Months) (30 days after Visit 4:-7, +14 days).</u> The subject diary will be collected and reviewed with all subject's parents/legal guardian. A blood sample of approximately 5ml will be collected to evaluate the level of bactericidal antibodies.</p> <p>Visit 6 will be appointed for when subject reaches 24 months of age (+/-60 days).</p> <p><u>Visit 6 (24 months of age; +/- 60 days).</u> A blood sample of approximately 5ml will be collected to evaluate the level of bactericidal antibodies. Any symptoms or medical events that are new or changed since previous visit, such as SAEs, medically attended AEs or AEs leading to premature withdraw, and medications used to treat them.</p> <p>All blood draws should be delayed in case the subjects received oral or parenteral antibiotic treatment in the 7 days prior to the scheduled blood draw.</p>		
<p>Study Vaccines:</p> <p>The study Novartis MenACWY vaccine is obtained by extemporaneous mixing just before injection of the lyophilized Men A component to be re-suspended with the liquid Men CWY component. After reconstitution the MenACWY vaccine will have the following composition per 0.5 mL of injectable solution:</p>		

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Table 3: Composition of Novartis MenACWY Conjugate Vaccine

Name of Ingredients	Quantity per dose
CRM ₁₉₇ -MenA conjugate	10 µg MenA, 12.5 – 33 µg CRM ₁₉₇
CRM ₁₉₇ -MenC conjugate	5 µg MenC, 6.5 - 12.5 µg CRM ₁₉₇
CRM ₁₉₇ -MenW conjugate	5 µg MenW, 3.3 – 10 µg CRM ₁₉₇
CRM ₁₉₇ -MenY conjugate	5 µg MenY, 3.3 – 10 µg CRM ₁₉₇
Sodium chloride	4.5 mg
Sucrose	12.5 mg
Sodium phosphate buffer	10 mM
Potassium dihydrogen phosphate	5 mM
Water for injection	qS to 0.5 mL

Primary Endpoint(s): Immunogenicity Endpoint(s).

No specific criteria are established to assess adequacy of the antibody persistence. All analyses will be run descriptively.

- Percentage of subjects with hSBA ≥ 8 at Visits 5 and 6
- hSBA GMTs at Visits 5 and 6
- Percentage of subjects with rSBA ≥ 8 at Visits 5 and 6
- Percentage of subjects with rSBA ≥ 128 at Visits 5 and 6

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<ul style="list-style-type: none"> • rSBA GMTs at Visits 5 and 6 <p>Safety Endpoint(s):</p> <p>Percentage of subjects with:</p> <ul style="list-style-type: none"> • Immediate reactions reported within 30 minutes after vaccination. • Solicited local and systemic adverse events from Day 1 to Day 7 following each vaccination • Medically-attended unsolicited AEs and AEs leading to premature withdraw from Day 1 to Visit 6 (at 24 months of age) • SAEs from Day 1 to Visit 6 (at 24 months of age) 		
<p>Statistical Analyses:</p> <p>There is no statistical hypothesis associated with the immunogenicity objective. All analyses will be run descriptively.</p> <p>The primary objective is to evaluate the persistence of the antibody response against <i>N. meningitidis</i> serogroups A, C, W and Y at approximately 1 year after completion of a 4-dose infant vaccination. This persistence will be summarized as the percentage of subjects with a titer ≥ 8 (hSBA) or with a titer ≥ 8 and ≥ 128 (rSBA) along with associated two-sided 95% Clopper-Pearson confidence intervals.</p> <p>The antibody titers will be summarized using GMTs with two-sided 95% confidence intervals constructed by exponentiation (base 10) of the means and confidence limits of the logarithmically transformed (base 10) antibody titer. Moreover the geometric mean ratios (GMR) between visit 6 (1 year after full vaccination) and visit 5 (1 month after full vaccination) will be provided along with the 2-sided 95% confidence intervals.</p> <p>Approximately 135 subjects will be enrolled in this study providing approximately 100 evaluable subjects, assuming a 25% drop-out. The sample size is based on the number of subjects requested and agreed with South Korean Health Authorities for this persistence</p>		

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study.

With 100 evaluable subjects, the 95% confidence limits of the observed percentages of subjects with hSBA titer ≥8 or rSBA titer ≥ 8 or ≥128 will be as presented in the following table.

Table 4: Calculated 95% Confidence Interval, Associated With Different Observed Percentages of Subjects

Observed percentage	95% confidence interval (Menveo® N=100)
50%	40%- 60%
60%	50%-70%
70%	61%-79%
80%	72%-88%
90%	84%-96%

Dependent on the point estimate, the length of the confidence interval will be 12% - 20%.

The analyses will be done on the Full Analysis Set (FAS population).

Additional details will be described in the statistical analysis plan.

Interim Analysis:
The interim analysis is not applicable in this study.

Data Monitoring Committee:
The Data Monitoring Committee is not Applicable for this study.

Time and Events Table – Treatment Period

Visit Type		Clinic Visit	Phone Call	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Clinic Visit	Clinic Visit	
		1	3	61	63	121	123	301	304	331	661	
		n/a	-1/+1	+/-7	n/a	+/-7	-1/+1	+14	-1/+1	-7/+14	+/-60	
		2		4		6		12		13	24	
Visit Number		1		2		3		4		5	6	
Study Event	References											
Study Treatment												
Vaccination	Section 5.2	X		X		X		X				
Screening and Safety												
Inform Consent *	Section 5.1.1	X ^a										
Medical History	Section 5.1.2	X										
Physical Exam	Section 5.1.2 and 5.3.1	X ^b		X		X		X	•	X	X	
Exclusion/Inclusion Criteria	Section 4.0	X ^c		X		X		X		X	X	
30 Minutes Post Injection Assessment	Section 5.2.1	X		X		X		X				
Subject Diary Dispensed/Training	Section 5.2.1	X		X		X		X				
Subject Diary Reminder Call	Section 5.2.2		X		X		X		X			
Subject Diary Review/ Collect	Section 5.3.1			X		X		X		X		
Assess all solicited AEs	Section 7.1.1 and 7.1.3	X ^d		X ^d		X ^d		X ^d		X ^d		

Visit Type		Clinic Visit	Phone Call	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Clinic Visit	Clinic Visit
Study Day		1	3	61	63	121	123	301	304	331	661
Visit Window (Days)		n/a	-1/+1	+/-7	n/a	+/-7	-1/+1	+14	-1/+1	-7/+14	+/-60
Months of age		2		4		6		12		13	24
Visit Number		1		2		3		4		5	6
Study Event	References										
Assess SAEs	Section 7.1.4	X ^c		X ^c		X ^c		X ^c		X ^c	X ^c
Medically attended AEs, AEs leading to withdrawal	Section 7.1.4.1 and 7.1.3			X ^c		X ^c		X ^c		X ^c	X ^c
Immunogenicity											
Serology blood draw	Section 3.5.									X	X

Notes:

- Confirm consent form(s) signed prior to any procedures. * May be collected up to 5 days prior to vaccination on day 1.
- Physical examination must be performed by a qualified healthcare professional.
- Procedures to be performed prior to vaccination.
- Only solicited adverse event (AE) occurred during the day of each vaccination and for the following 6 days will be reported by the subject on a subject diary.
- SAEs, medically attended AE and AEs leading to study or vaccine withdrawal will be collected through Day 661. Please see [section 6.6](#) for greater detail regarding methods for SAE and AEs leading to study or vaccine withdrawal collection

LIST OF ABBREVIATIONS

AE	Adverse Event
BCDM	Biostatistics and Clinical Data Management
BLA	Biologic License Application
CI	Confidence Interval
CRO	Contract Research Organization
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDT	Electronic Data Transfer
EMA	European Medicines Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GMT	Geometric Mean Titer
hSBA	Human Complement Serum Bactericidal Assay
rSBA	Rabbit Complement Serum Bactericidal Assay
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IM	Intramuscular
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MFDS	Ministry of Food Drugs and Safety
PP	Per Protocol
SAE	Serious Adverse Event
SDA	Source Data Agreement
SOP	Standard Operating Procedure
TV	Termination visit

1.0 BACKGROUND AND RATIONALE

1.1 Background

Meningococcal disease is caused by a gram-negative diplococcus, *Neisseria meningitidis*. Invasive infection by *N. meningitidis* usually results in bacteremia and/or meningitis, and can be complicated by purpuric rash (meningococemia), arthritis, myocarditis, pericarditis, endophthalmitis, or pneumonia. This disease often cannot be distinguished clinically from other forms of acute bacterial meningitis and sepsis caused by *Haemophilus influenzae* or *Streptococcus pneumoniae*. The signs of meningococcal meningitis in adults include headache, stiff neck, fever, chills, malaise, and prostration. Asymptomatic colonization of the upper respiratory tract by encapsulated *N. meningitidis* is common, yet only a small percentage of colonized persons develop disease. Transmission is thought to be via droplets of respiratory tract secretions.

Novartis Vaccines and Diagnostics has developed a quadrivalent conjugate vaccine aimed at preventing disease in infants and older age groups due to *Neisseria meningitidis* serogroups A, C, W, and Y. Serogroup prevalence varies with geography, time of year, and age group. Currently, serogroup B and C strains are most prevalent in Europe, and serogroup B, C and Y strains are most prevalent in North America.¹

N. meningitidis serogroup A strains are responsible for large epidemics of bacteremia and meningitis in sub-Saharan Africa, with attack rates as high as 500 to 1000 per 100,000 population.² Outbreaks due to serogroup W have also recently been reported in the same geographic location and among Hajj pilgrims.

Meningococcal vaccines containing polysaccharides of serogroups A, C, W and Y were licensed to control meningococcal epidemics, but their use is limited by poor immune response and protection for young children, especially those younger than 2 years of age (the group that is generally at highest risk of disease). The available polysaccharide vaccines also do not induce immunologic memory and may trigger immunologic hyporesponsiveness, even in older individuals.

Novartis' meningococcal C conjugate vaccine (Men C, Menjugate), has been licensed in over 30 countries worldwide and has been successfully used in immunization campaigns in response to serogroup C meningococcal outbreaks in the United Kingdom and Quebec, Canada ([Trotter C, Lancet 2004; 364: 365-367](#)).¹² The development program for Novartis' Meningococcal ACWY conjugate vaccine (Novartis MenACWY, Menveo[®]) builds upon this experience and includes manufacturing methods similar to those employed for Menjugate. In brief, the vaccine synthesis involves production of sized oligosaccharides from each of the four meningococcal serogroups (A, C, W, and Y) and their individual conjugation to the protein carrier, CRM197. Therefore, the intent of this

program is to provide a meningococcal conjugate vaccine with broad serogroup coverage, protecting persons across all age groups, from infants through adults.

In 2010, Menveo[®], (Meningococcal ACWY Conjugate Vaccine) was licensed for use in adolescents and adults, 11 years of age and older in the United States.

On October 27, 2010, the Advisory Committee on Immunization Practices (ACIP) approved updated recommendations for the use of quadrivalent meningococcal conjugate vaccines in adolescents and persons at high risk for meningococcal disease (Recommendations of the Advisory Committee on Immunization Practices (ACIP). Morbidity and Mortality Weekly Report (MMWR). The two new recommendations approved are: (1) a booster dose at age 16 years in subjects immunized at 11 to 12 years of age and (2) a 2-dose primary series administered 2 months apart for persons aged 2 through 54 years with persistent complement component deficiency (e.g., C5--C9, properdin, factor H, or factor D) and functional or anatomic asplenia, and for adolescents with human immunodeficiency virus (HIV) infection.

Supplementary BLAs (sBLAs) for an expanded age indication in children (2-10 years of age) and infants (2-23 months of age) were approved in US in January 2011 and August 2013, respectively. In EU two variations for the same extensions were submitted in August 2011. The variation to expand age indication in children (2-10 years of age) was approved in April 2012. Currently MenACWY vaccine is registered for vaccination of adolescents and adults in more than 60 countries; many of these countries have also approved use in children (2-10 years of age) and infants (2-23 months of age).

1.2 Rationale

Novartis MenACWY (Menveo[®]) has been approved for use in people 2 months through 55 years of age in the United State and in people of 2 years and above in Europe and other countries, including the Republic of South Korea. In South Korea, the indication was extended in May 2014 to infants 2 months of age to 55 years, and as post commitment of indication change, the Regulatory Authorities of the Republic of South Korea, (MFDS) have requested data on immunogenicity persistence in the Korean children who received 4 doses of Menveo[®] at 2-4-6-12 months of age.

2.0 OBJECTIVES

2.1 Primary Objective(s)

Primary Safety Objective(s)

To assess the safety and tolerability of MenACWY administered at 2-4-6 and 12 months of age.

Primary Immunogenicity Objective(s)

1. To evaluate the persistence of the antibody response against *N. meningitidis* serogroups A, C, W and Y at approximately 1 year after completion of a 4-dose infant vaccination series (2, 4, 6 and 12 months of age) of MenACWY vaccine as measured by hSBA titers ≥ 8 .
2. To evaluate the persistence of the antibody response against *N. meningitidis* serogroups A, C, W and Y at approximately 1 year after completion of a 4-dose infant vaccination series (2, 4, 6 and 12 months of age) of MenACWY vaccine as measured by rSBA titers ≥ 8 and ≥ 128 .

2.1 Secondary Objective(s)

Secondary Immunogenicity Objectives

1. To describe hSBA titers ≥ 8 and hSBA GMTs against *N. meningitidis* serogroups A, C, W and Y 1 month after a full vaccination series at 2, 4, 6 and 12 months of age
2. To describe rSBA titers ≥ 8 and ≥ 128 rSBA and GMTs against *N. meningitidis* serogroups A, C, W and Y 1 month after a full vaccination series at 2, 4, 6 and 12 months of age
3. To evaluate the persistence of the antibody response against *N. meningitidis* serogroups A, C, W and Y at approximately 1 year after completion of a 4-dose infant vaccination series (2, 4, 6 and 12 months of age) of MenACWY vaccine as measured by hSBA GMTs and rSBA GMTs

3.0 STUDY DESIGN

3.1 Overview of Study Design

This is a Phase IV multicenter open label, post marketing commitment study to evaluate the persistence of antibody response in approximately 135 children 1 year after completion of series of Menveo[®] vaccination at 2-4-6-12 month vaccination. The study foresees 6 clinical visits, 2 blood draws (at 13 and 24 months) and 4 reminder phone calls. The subjects study participation is approximately 22 months.

Table 3.1-1 Overview of the study design

N Subjects	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	2-Months	4-Months	6-Months	12-Months	13- Months	24- Months
135	Menveo [®]	Menveo [®]	Menveo [®]	Menveo [®]	Blood draw	Blood draw

The informed consent will be obtained prior to any study-related procedures and subjects will be enrolled only after their eligibility for participation is confirmed by the investigator. All participants will receive 4 doses of Menveo[®] in an open label fashion. A total of two blood samples will be drawn from all subjects for immunogenicity evaluation at the following time points: 1 month after the fourth and last dose of Menveo[®] vaccine, (Visit 5, 13 months of age) and one during the last clinical visit (Visit 6, 24 months of age).

After each vaccination, all subjects will remain under medical supervision at the study site for at least 30 minutes to be monitored in case of a hypersensitivity reaction. Furthermore, subject's parent/legal guardian will be instructed on the completion of a subject diary, to record solicited local and systemic AEs and other solicited events (including body temperature and use of analgesics/antipyretics for prophylaxis or treatment), for 7 days, starting on the day of vaccination and continuing during each of the 6 days following vaccination. They will also be instructed to call the site if they develop any adverse event(s) of concern including those which require admission to a hospital or an emergency room or a visit to/by a doctor. In order to ensure proper completion of the subject diary four reminder calls will be carried out by the site staff 2 days after each vaccination visit (e.g. on Day 3).

Subject diary will be collected by study staff at the next clinical study visits until visit 5. The safety information obtained by study personnel will be recorded on the appropriate web based system referred to as Electronic Data Capture (EDC).

Site staff will record the following selected safety measures in the EDC:

- Solicited local adverse events: Injection site erythema, injection site induration, injection site tenderness (from Day 1 to Day 7 after each Men ACWY vaccination)
- Solicited systemic adverse events: Change in eating habits, sleepiness, irritability, vomiting, diarrhea, fever (from Day 1 to Day 7 after each Men ACWY vaccination).
- Unsolicited Adverse Events: All medically-attended unsolicited AEs and AEs leading to premature withdrawal will be collected (From Day 1 of the study and orally during the last clinical visit)
- Serious AEs: All SAEs will be collected from day 1 to end of study. SAEs will be monitored until resolution and/or the cause is identified (if a SAE remains unresolved at study termination, a clinical assessment will be made by the investigator and the Novartis medical monitor to determine whether continued follow up of the SAE is warranted) Medications used to treat any medically-attended AE and SAE will be collected from Day 1 of the study and during the last clinical visit.
- Note that all medically-attended unsolicited AEs, AEs leading to premature withdraw and all the medication used to treat them, these data will be captured by interviewing the subject and/or subjects' parents/guardian (as applicable) during clinic visits.

3.2 Study Period

Each subject should expect to participate in the study for 22 months, from the time of enrolment through the last study visit.

3.3 Blinding Procedures

The trial is designed as an open label study; therefore blinding procedures are not applicable.

3.4 Data Collection

3.4.1 Data Collected from Subjects

The following data will be collected from each subject over the duration of their study participation:

- Demographic Information (Date of Birth, Sex, Weight, Height)

- Adverse Events Seriousness, Date of Onset, Date of Resolution, Frequency, Severity, Actions Taken, Outcome, Relationship to Study Vaccine
- Medical History that may be relevant to subject eligibility for study participation such as prior vaccinations
- Concomitant Medications
- Vaccination record (Pre-Vaccination Body Temperature, Date of Vaccination, Injection Site)
- Study termination (Reason(s) for ending study participation or Reason(s) for early termination)

All data collected must only be identified using the Novartis Subject ID, as described in [section 5.1.4, Randomization](#).

3.4.2 Tools Used for Data Collection

Data will be recorded in the Subject Diary and collected on Case Report Forms (CRFs).

Subject Diary

Paper Diaries (pDiaries) hereafter referred to as Subject Diaries will be the only source document allowed for solicited local and systemic adverse events (including body temperature measurements), starting after the initial 30 minute post-vaccination period at the clinic. The following additional rules apply to documentation of safety information collected in the Subject Diary.

1. No corrections or additions to the information recorded by the subject within the Subject Diary will be allowed after it is delivered to the site.
2. Any blank or illegible fields on the Subject Diary must be described as missing in the CRF.

Case Report Forms

This study utilizes Case Report Forms (CRFs) to collect study-related data from each subject. A qualified site staff member(s) is required to enter subject data in the CRFs in English based on the medical information available in each subject's source record.

Data should be entered into the CRF in a timely fashion following each subject's clinic visit, study procedure, or phone call. Each subject's CRF casebook will be compared with the subject's source records by a Novartis-approved study monitor (or designee) over the duration of the study in order to ensure data collection accuracy.

The following additional rules apply to documentation of Subject Diary information collected in the CRFs:

1. The site must enter all readable entries in the Subject Diary into the CRF, including those values that may be biologically implausible (e.g. body temperature: 400°C).
2. Any illegible or implausible data should be reviewed with the parent(s)/legal guardian(s). If an underlying solicited or unsolicited adverse event is described on review with the subject, this should be described in the source document and reported as an unsolicited adverse event in the Adverse Event CRF (e.g., if the subject above confirms body temperature of 40°C on the day in which body temperature: 400°C was written into his/her Subject Diary, this fever of 40°C should be recorded in the Adverse Event CRF).
3. Any newly described safety information (including a solicited adverse event) must not be written into the Subject Diary and must be described in the study file as a verbally reported adverse event. Any adverse event reported in this fashion must be described as an unsolicited adverse event and therefore entered on the Adverse Event CRF.

3.5 Collection of Clinical Specimens

During the study will be collected 2 blood draws approximately at 13 and 24 months (Visit 5 and Visit 6). Detailed information about the laboratory assays is to be provided in [section 7.0, Assessments](#).

Processing of each specimen should be completed by a qualified site member and in accordance with the study-specific Clinical Specimen Laboratory Manual. Testing of clinical specimens will be performed by a Novartis or designated laboratory. Refer to the study-specific Clinical Specimen Laboratory Manual for additional details.

Blood Specimens

An approximately 5 mL sample of blood will be drawn from all subjects at visits 5 and 6; a 5 mL sample of blood will provide the necessary serum volume for the serology assays (approximately half of the blood draw volume). The blood volume will not exceed 5 mL at each time point.

The blood will be used for immunological assays See [section 7.0, Assessments](#) for additional details.

The total amount of blood collected over the study period per subject will be 10 mL.

3.6 Stopping/Pausing Guidelines

There are no predetermined stopping rules other than circumstances for which subjects may not be eligible for additional study vaccinations as described in [section 4.0, Selection of Study Population](#) or may be withdrawn from the study according to the best interests of the subject as described in [section 3.8, Premature Withdrawal from Study](#).

3.7 Data Monitoring Committee

Not applicable for this study.

3.8 Premature Withdrawal from Study

Subjects may withdraw at any time, or be dropped from the study at the discretion of the investigator should any untoward effects occur and/or for safety reasons. In addition, a subject may be withdrawn by the investigator or the Sponsor if he/she violates the study plan or for administrative reasons. The investigator or study coordinator must notify the Sponsor immediately when a subject has been withdrawn due to an adverse event.

The circumstances above are referred to as premature withdrawal from the study, and the reason for premature withdrawal should be clearly documented and detailed in the source documentation. The investigator should make every attempt to evaluate the subject's safety, including resolution of ongoing AEs, at the time of premature withdrawal. If a subject wants to withdraw from the study before all doses are administered or prior to the last planned study visit, the subject will be asked to be followed for safety for the duration of the study. When a subject withdraws, or is withdrawn, from the study, the procedures described in [section 5.5.1, Early Termination Visit](#) should be completed if possible.

The reasons for premature withdrawal from the study include: adverse event, death, withdrawal of consent, lost to follow-up, administrative reason, and protocol deviation. These reasons are described in greater detail below.

Adverse Event

For any subject withdrawn from study participation prior to the planned Study Termination Visit, it is important to determine if an AE was associated with the reason for discontinuing the study. This AE must be identified on the AE CRF page by indicating "Withdrawn from study due to AE". Any ongoing AEs at the time of study withdrawal must be followed until resolution or stabilization.

Subjects who develop a serious adverse event (SAE) judged to be possibly or probably related to the study vaccine, including hypersensitivity reactions, should not receive subsequent vaccination.

Death

For any subject withdrawn from study participation due to death, this should be noted on the Study Termination CRF page and the associated SAE that led to the death must be reported.

Withdrawal of consent

The subject parent(s)/legal guardian(s) can withdraw consent for participation in the study at any time without penalty or loss of benefit to which the subject is otherwise entitled. Reason for early termination should be deemed as “withdrawal of consent” if the subject withdraws from participation due to a non-medical reason (i.e., reason other than AE). If the subject parent(s)/legal guardian(s) intends to withdraw consent from the study, the investigator should clarify if the subject will withdraw completely from the study or if the subject will continue study participation for safety, or a subset of other study procedures. If the subject requests complete withdrawal from the study, no further study interventions will be performed with the subject.

Lost to Follow-Up

For subjects who fail to show up for final visits (clinic or telephone contacts), or for three consecutive visits, study staff are encouraged to make at least three documented attempts to contact the subject by telephone and at least one documented written attempt to contact the subject parent(s)/legal guardian(s) to encourage the completion of study termination procedures. These efforts to contact the subject should be recorded in the source document. The termination date for the subject to be captured on the Study Termination CRF page is the date of the last successful contact (clinic visit or telephone) with the subject.

Administrative Reason

Examples for subjects withdrawn from the study due to administrative reason can include: Sponsor decision to terminate the study, subject meeting a pre-specified withdrawal criterion, subject discontinuation for insurance issues, moving, no time, etc. This reason should be noted in the Study Termination CRF page and any ongoing AEs at the time of study withdrawal must be followed until resolution/stabilization.

If the clinical study is prematurely terminated by the Sponsor, the investigator is to promptly inform the study subjects and local EC/IRB and should assure appropriate therapy and follow up for the subjects. All procedures and requirements pertaining to the archiving of study documents should be followed. All other study materials (study medication/vaccines, etc.) must be returned to the Sponsor.

For subjects who are withdrawn from the study due to receipt of an excluded medication/vaccination or due to significant protocol non-compliance, this reason should be noted in the Study Termination CRF page.

Protocol Deviation

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. In general, subjects associated with protocol deviations may remain in the study unless continuation in the study jeopardizes the subject's health, safety, or rights.

Investigators will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a change to the protocol would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/EC and health authorities it cannot be implemented.

3.9 End of Study

Most clinical trials intended to support the efficacy/immunogenicity and safety of an Investigational Product proceed to full completion of planned sample size accrual.

Evaluation of the primary and/or secondary immunogenicity/efficacy objectives requires the testing of biological samples from the study subjects, which can only be completed after all samples are collected. The last samples for the analysis of the primary and/or secondary objectives will be taken at visit 6. For the purpose of this protocol, end of study is defined as the completion of the testing of such biological samples, to be achieved no later than 8 months after collection of the last biological sample visit 6.

4.0 SELECTION OF STUDY POPULATION

4.1 Inclusion Criteria

In order to participate in this study, all subjects must meet ALL of the inclusion criteria described.

1. Healthy male and female 2 month-old infants (55 – 89 days) on the day of consent.
2. Infants whose parents or legal guardians have voluntarily given written informed consent after the nature of the study has been explained according to local regulatory requirements, prior to study entry.
3. Infants whose parents or legal guardians can comply with study procedures including follow-up

Prior to receipt of study vaccination, subjects must be evaluated to confirm that they are eligible for subsequent vaccination. If subjects do not meet any of the original inclusion criteria listed above, they should not receive additional vaccinations.

4.2 Exclusion Criteria

Each subject must not have/have been:

1. previously received any meningococcal A, C, W and Y vaccines.
2. previous confirmed or suspected disease caused by *N. meningitidis* or who have had household contact with and/or intimate exposure to an individual with laboratory confirmed *N. meningitidis* infection at any time since birth.
3. progressive, unstable or uncontrolled clinical conditions.
4. a history of anaphylactic shock, asthma, urticaria or other allergic reaction after previous vaccinations or known hypersensitivity to any vaccine component, such as latex allergy.
5. experienced significant acute or chronic infection within the previous 7 days or have experienced fever (temperature $\geq 38.0^{\circ}\text{C}$ [100.4°F]) within the previous 3 days.
6. any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination.
7. received treatment with systemic administration corticosteroids (PO/IV/IM) for more than 14 consecutive days from birth.

8. ever received blood, blood products and/or plasma derivatives or any parenteral immunoglobulin preparation (including Hepatitis B immune globulin) at anytime since birth and for the full length of the study.
9. any bleeding disorder which is considered as a contraindication to intramuscular injection or blood draw.
10. any condition which, in the opinion of the investigator, might interfere with the results of the study or pose additional risk to the subject due to participation in the study.
11. received or are planning to receive any investigational or non-registered medicinal product from birth and throughout the study.
12. received oral or parenteral antibiotic treatment in the 3 days prior to the scheduled blood draw (topical antibiotics are acceptable, including antibiotic eye drops).
13. relatives of site research staff working on this study.

Prior to receipt of study vaccination, subjects must be evaluated to confirm that they are eligible for subsequent vaccination. At subsequent vaccinations, if subjects meet any of the original exclusion criteria listed above (with exception exclusion criteria 1, previous received the study vaccine), they should not receive additional vaccinations.

4.3 Criteria for Delay of Vaccination

There may be instances when individuals meet all eligibility criteria for vaccination yet have a transient clinical circumstance which may warrant delay of vaccination:

- experienced significant acute or chronic infection within the previous 7 days or have experienced fever (temperature $\geq 38.0^{\circ}\text{C}$ [100.4°F]) within the previous 3 days
- or use of antipyretics and/or analgesic medications within 24 hours prior to vaccination.

Under such circumstances, a subject may be considered eligible for study enrolment after the appropriate window for delay has passed and inclusion/exclusion criteria have been rechecked, and if the subject is confirmed to be eligible.

5.0 STUDY PROCEDURES

The sections that follow provide an overview of the procedures that are to be followed in enrolling, evaluating, and following subjects who participate in this clinical study. Visits can be either clinic visits or safety follow-up telephone calls, as specified in the Table below and in the [Time and Events Table](#).

Table 5.0-1 Study Procedures

Visit Category	Procedures
Pre-vaccination Clinic Visit(s)	Section 5.1 describes procedures to be followed prior to study vaccination: informed consent/assent, screening, enrolment, and randomization
Vaccination Clinic Visit(s)	Section 5.2 describes procedures to be followed during each clinic visit involving vaccination: vaccination, post-vaccination procedures, and post-vaccination reminder calls
Post-vaccination Visit(s)	Section 5.3 describes follow-up clinic visits and safety follow-up calls
Unscheduled Visit(s)	Section 5.4 describes possible procedures to be followed at unscheduled clinic visit
Study Termination Visit	Section 5.5 describes procedures to be followed at the last study visit for a subject (may include early termination visit)

5.1 Pre-vaccination Clinic Visit(s)

This section describes the procedures that must be performed for each potential subject prior to vaccination, including obtaining informed consent/assent, screening, enrolment and randomization.

5.1.1 Informed Consent/Assent

"Informed consent" is the voluntary agreement of an individual or his/her legal guardian(s) to participate in research. Consent must be given with free will of choice, and without undue inducement. The individual must have sufficient knowledge and understanding of the nature of the proposed research, the anticipated risks and potential benefits, and the requirements of the research to be able to make an informed decision.

Informed consent following local IRB/EC guidance **must** be obtained before conducting any study-specific procedure (i.e., all of the procedures described in the protocol). The

process of obtaining informed consent should be documented in the subject source document in addition to maintaining a copy of the signed and dated informed consent.

Informed consent of the parent(s)/legal guardian(s) and assent of subject following local IRB/EC guidance **must** be obtained before conducting any study-specific procedures (i.e., all of the procedures described in the protocol). The process of obtaining informed consent and assent should be documented in the subject source document in addition to maintaining a copy of the signed and dated informed consent. Additional specifics regarding the informed consent and assent processes are located in [section 13.2, Informed Consent Procedures](#).

If a subject parent(s)/legal guardian(s) is unable to read, an impartial witness should be present during the entire informed consent discussion. An impartial witness is defined as a person who is independent from study conduct, who cannot be unfairly influenced by those involved with the study, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject parent(s)/legal guardian(s) and after the subject parent(s)/legal guardian(s) has verbally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject parent(s)/legal guardian(s) and that informed consent was freely given by the subject parent(s)/legal guardian(s).

5.1.2 Screening

After an individual has consented to participate in the study and informed is signed, that individual will be given a unique Screening Number manually created by the investigator. The subject's unique Screening Number will be documented in the Screening and Enrolment log. The eligibility of the subject will be determined based on the inclusion and exclusion criteria listed in [section 4.0, Selection of Study Population](#) and evaluated during this screening procedure.

Prior to study enrolment, demographic data will be collected from the subject, including: age, sex, race, height, weight and ethnicity. Medical history will also be collected, including but not limited to any medical history that may be relevant to subject eligibility for study participation such as prior vaccinations, concomitant medications, and previous and ongoing illnesses or injuries. Relevant medical history can also include any medical history that contributes to the understanding of an adverse event that occurs during study

participation, if it represents an exacerbation of an underlying disease/pre-existing problem.

Review of systems is a structured interview that queries the subject parent(s)/legal guardian(s) as to any complaints the subject has experienced across each organ system. This will be performed before enrolment and used to guide physical examination.

If applicable, prior and concomitant medications or vaccinations taken prior to start of study should be collected (refer to [section 6.5, Prior and Concomitant Medications and Vaccines](#) for further details).

Collect vital signs, including heart rate, temperature (this data is to be recorded in the source documents only). Vital signs measurements can be performed by a trained health care professional.

A general physical examination is to be performed by a qualified health care practitioner. “Qualified health care practitioner” refers to any licensed health care professional who is permitted by institutional policy to perform physical examinations and who is identified within the Study Staff Signature Log.

These data will be written in the source document (see [section 9.1, Source Documentation](#)). Should the physical assessment reveal any abnormal values or events, these must be documented in the CRF Adverse Events Form.

In the event that the individual is determined ineligible for study participation, he/she is considered a screen failure. The reason for screen failure must be documented in the Screening and Enrolment log. If the individual is determined to be eligible for the study, he/she will be enrolled into the study.

5.1.3 Enrolment

After signing the informed consent form, if an individual is determined to be eligible for study participation, the investigator will enroll the subject and enter the Screening Number into the EDC system.

5.1.4 Randomization

This is a non-randomized study. Enrolled subjects will be manually assigned a unique Subject ID. The Subject ID will be the subject’s unique identification number for all CRFs and associated study documentation that will be used for duration of the study. The Screening Number ceases to be used and remains in the Screening and Enrolment Log only.

If for any reason, after enrolment the subject fails to undergo the study procedures, this is an Early Termination and the reason should be recorded in source document as specified in the Source Data Agreement. The information on these Early Termination subjects should be kept distinct in the source documentation from subjects who are screen failures, as described in [section 5.1.2, Screening](#).

5.2 Vaccination Clinic Visit(s)

Vaccination will be performed on day 1, day 61, day 121 and day 301. For studies which have visits for concomitant vaccinations or treatments, see [section 6.5, Prior and Concomitant Medications and Vaccines](#) for those visit procedures.

After completing the pre-vaccination procedures on day 1, administer the vaccine to the subject according to the procedures described in [section 6.3, Vaccine Preparation and Administration](#). Prior to administration of each vaccination, confirm that the subject is eligible for additional study vaccinations and does not meet any criteria for delaying additional study vaccinations as described in [section 4.0, Selection of Study Population](#).

5.2.1 Post-vaccination Procedures

The following post-vaccination procedures will be performed on day 1, day 61, day 121 and day 301.

After vaccination, the subject will be observed for at least 30 minutes including observation for, solicited adverse events, and body temperature measurement. Record all safety data collected during this time in the subject's source document.

A Subject Diary will be used in this study to document solicited adverse events. The Subject Diary is the only source for collection of these data; therefore, it is critical that the subject parent(s)/legal guardian(s) completes the Subject Diary correctly. The subject parent(s)/legal guardian(s) should be trained on how and when to complete each field of the Subject Diary.

The subject parent(s)/legal guardian(s) should be trained on how to measure local solicited adverse events and body temperature. The measurement of solicited local adverse events is to be performed using the ruler provided by the site.

The subject parent(s)/legal guardian(s)] should be instructed how to perform body temperature measurement using the thermometer provided by the site. If the subject feels unusually hot or cold during the day, the subject parent(s)/legal guardian(s) should check body temperature. If the subject has fever, the highest body temperature observed that day should be recorded in the Subject Diary.

Subject Diary training should be directed at the individual(s) who will perform the measurements of adverse events and who will enter the information into the Subject Diary. This individual may not be the subject parent(s)/legal guardian(s), but if a person other than the subject parent(s)/legal guardian(s) enters information into the Subject Diary, this person's identity must be documented in the Subject Diary and in the subject's source record. Any individual that makes entries into the Subject Diary must receive training on completion of the Subject Diary at the time of the visit. This training must be documented in the subject's source record.

The site should schedule the next clinic visit with the subject parent(s)/legal guardian(s).

The subject parent(s)/legal guardian(s) should be reminded of the next planned study activity. The subject parent(s)/legal guardian(s) will be reminded to complete the Subject Diary and to contact the site if there are any questions, and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit or to a visit to/by a doctor or is of concern.

5.2.2 Post-vaccination Reminder Calls

Subject Diary reminder calls will be performed on day 3 after each vaccination. The purpose of this call is to remind the subject parent(s)/legal guardian(s) about completion of the Subject Diary. The call follows the Subject Diary Reminder Telephone Call Script provided to the site. The subject parent(s)/legal guardian(s) should be reminded to contact the site via the telephone number provided in the informed consent to discuss medical questions.

5.3 Post-vaccination Visit(s)

Post-vaccination visits will be performed on day 331 and on day 661.

5.3.1 Follow-up Clinic Visit(s)

During the follow-up clinic visit, the Subject Diary will be reviewed. No changes to the information recorded within the Subject Diary are permissible. For details on the Subject Diary see [sections 3.4.2, Tools Used for Data Collection](#) and [5.2.1, Post-vaccination Procedures](#). The subject parent(s)/legal guardian(s) will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken/received in the time since the last clinic visit. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. Adverse events reported by the subject parent(s)/legal guardian(s) at this follow-up clinic visit must be

recorded in the subject's source document and on an Adverse Events CRF, as specified in [section 7.1, Safety Assessment](#).

Perform a brief symptom-directed physical examination if necessary according to symptoms the subject has reported. This is a physical examination that will include an examination of organ systems that are relevant to the investigator based on review of the subject's reported adverse events, concomitant medication and body temperature. The physical assessment must be performed by the investigator or designee of the investigator, who is qualified to perform a physical assessment in accordance with their institutional policy. Corresponding information is documented in the subject's source document and CRF(s).

A blood sample will be collected at Visit 5 and Visit 6, as specified in [section 3.5](#).

The site should schedule the next clinic visit (if applicable) with the subject and parent(s)/legal guardian(s).

The subject parent/legal guardian(s) will receive a written reminder of the next planned study activity. The subject parent(s)/legal guardian(s) will be reminded to complete the Subject Diary and to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

5.3.2 Safety Follow-up Calls

There are no safety follow up calls in this study.

5.4 Unscheduled Visits

An unscheduled visit describes a non-routine study visit triggered by a specific event. These could include anticipated or unanticipated adverse events or interventions.

5.5 Study Termination Visit

The study termination visit will occur on day 661. The termination visit may be a clinic visit or a telephone call. The date of termination is the date of the last contact (clinic visit or telephone call) in which the subject's health status was assessed or, in cases where the subject does not agree to any further safety follow-up, it is the date consent is withdrawn. This date should be recorded on the termination CRF page. For visit procedures to be performed for a subject whose planned study participation ends prematurely, please see [section 5.5.1, Early Termination Visit](#).

At the clinic visit or during the telephone call, the following procedures will be performed:

- Review of the safety information that includes review of Subject Diary, review of systems, interview of subject parent(s)/legal guardian(s) to collect any medically attended adverse events, AEs leading to withdrawal, SAEs
- Interview of subject parent(s)/legal guardian(s) to collect concomitant medications/ vaccinations associated with the AEs listed above, Symptom-directed physical assessment is to be performed as needed (including measurement of vital signs, body temperature and a check of general appearance)
- Collection of the last blood sample as specified in [section 3.5](#) and [section 4.3](#).
- The site will review with the subject parent(s)/legal guardian(s) the plan of when information relating to the subject's participation in the study may be available (e.g., study results, treatment assignments). It will also be discussed how information relating to the subject's participation in the study will be shared with the subject's healthcare provider, if the subject parent(s)/legal guardian(s) chooses to share this information

The site will complete the termination CRF page and this will mark the completion of the subject's participation in the study.

5.5.1 Early Termination Visit

When a subject is withdrawn from treatment or withdraws from the study, the investigator will notify the Sponsor and, when possible, will perform the procedures listed below. The reason(s) for the early termination will be included in the subject's source documentation. If the Early Termination Visit is a telephone call, collect as much information as possible. Early Termination Visits include subjects who were enrolled but not treated.

At the clinic visit or during the telephone call, the following procedures will be performed:

- Review of the safety information that includes review of Subject Diary (if applicable), review of systems, interview of subject and/or parent(s)/legal guardian(s) to collect unsolicited adverse events occurring within 30 days of vaccination, medically attended adverse events, AEs leading to withdrawal, SAEs.
- Interview of subject and/or parent(s)/legal guardian(s) to collect concomitant medications/ vaccinations associated with the above AEs.
- Symptom-directed physical assessment is to be performed as needed (including measurement of vital signs, body temperature and a check of general appearance).

The site will review with the subject parent(s)/legal guardian(s) the plan of when information relating to the subject's participation in the study may be available (e.g., study results, treatment assignments). It will also be discussed how information relating to the subject's participation in the study will be shared with the subject's healthcare provider, if the subject parent(s)/legal guardian(s) chooses to share this information.

The site will complete the termination CRF page and this will mark the completion of the subject's participation in the study.

6.0 TREATMENT OF SUBJECTS

All vaccines associated with this study are to be stored separately from other vaccines and medications in a secure location under appropriate storage conditions with temperature monitoring. **All vaccines associated with this study must be checked for expiration date prior to use. Expired vaccines must not be administered to subjects.**

6.1 Study Vaccine(s)

The term ‘study vaccine’ refers to those vaccines provided by the Sponsor, which will be evaluated as part of the study objectives. The study vaccines specific to this study are described below. Novartis MenACWY is licensed in South Korea in people from 2 years up to 55 years but Korean MFDS has recently extended the indication also in infants of 2 months of age.

Novartis MenACWY is provided in the form of:

- MenA conjugate component: One vial containing a lyophilized powder of the drug substance, MenA-CRM, as well as sucrose and potassium dihydrogen phosphate
- MenCWY conjugate component: One vial containing the drug substances MenC-CRM, MenW-CRM, and MenY-CRM conjugates, as well as sodium chloride, sodium phosphate buffer, and water for injection (WFI).

The vaccine is prepared by reconstituting the lyophilized MenA component with the liquid MenCWY component. The final formulation contains 10-5-5-5 µg per oligosaccharide of *N. meningitidis* serogroups A, C, W, and Y respectively, without adjuvant. The vaccine must be administered immediately after reconstitution. Novartis MenACWY is intended for storage at +2°C to +8°C and should not be frozen.

Table 6.1-1: Composition of Reconstituted Novartis MenACWY for 0.5 mL/Dose of Injectable Solution

Name of Ingredient	Quantity Per Dose (0.5 mL)	Function
Active Substances*		
MenA-CRM	10 µg MenA + 16.7 to 33 µg CRM	Antigen + carrier protein
MenC-CRM	5 µg MenC + 7.1 to 12.5 µg CRM	Antigen + carrier protein
MenW-CRM	5 µg MenW + 3.3 to 8.3 µg CRM	Antigen + carrier protein
MenY-CRM	5 µg MenY + 5.6 to 10 µg CRM	Antigen + carrier protein
Excipients		
Sodium chloride	4.5 mg	Tonicity modifying agent
Sodium phosphate buffer	10 mM	pH buffering agent
Sodium dihydrogen phosphate	2.5 mM (0.345 mg/mL)	
Disodium hydrogen phosphate dihydrate	7.5 mM (1.335 mg/mL)	
Potassium dihydrogen phosphate	5 mM (0.68 mg/mL)	
Sucrose	12.5 mg	Lyophilization bulking, tonicity modifying agent and stabilizer
WFI	Qs to 0.5 mL	Solvent

6.2 Non-Study Vaccines

The term ‘non-study vaccine’ refers to those vaccines which will be intentionally given to study subjects but not formally included in the analysis of study objectives. The Sponsor will not provide any non-study vaccines.

6.3 Vaccine Preparation and Administration

The investigator or designee will be responsible for oversight of the administration of vaccine to subjects enrolled in the study according to the procedures stipulated in this study protocol. All vaccines will be administered only by personnel who are qualified to perform that function under applicable local laws and regulations for the specific study site.

Detailed vaccine preparation and administration instructions will be provided to investigators in the Protocol Ancillary Document prior to study start.

PRECAUTIONS TO BE OBSERVED IN ADMINISTERING STUDY VACCINE:

Prior to vaccination, subjects must be determined to be eligible for study vaccination and it must be clinically appropriate in the judgment of the investigator to vaccinate.

Eligibility for vaccination prior to first study vaccine administration is determined by evaluating the entry criteria outlined in protocol [sections 4.1, Inclusion Criteria and 4.2, Exclusion Criteria](#).

Eligibility for subsequent study vaccination is determined by following the criteria outlined in [section 4.3, Criteria for Delay of Vaccination](#).

Eligibility for non-study vaccines should be determined by the investigator, pending the review of the package insert of the relevant vaccine.

Study vaccines should not be administered to individuals with known hypersensitivity to any component of the vaccines.

Standard immunization practices are to be observed and care should be taken to administer the injection intramuscularly. Before administering vaccine, the vaccination site is to be disinfected with a skin disinfectant (e.g., 70% alcohol). Allow the skin to dry. **DO NOT inject intravascularly or intragluteally.**

As with all injectable vaccines, trained medical personnel and appropriate medical treatment should be readily available in case of anaphylactic reactions following vaccine administration. For example, epinephrine 1:1000, diphenhydramine, and/or other medications for treating anaphylaxis should be available.

6.4 Vaccine Administration Error or Overdose of Vaccine

Vaccine administration error is defined as receiving a dose of study vaccine that was not reconstituted as instructed or administered by a different route from the intended route of administration. An overdose of study vaccine (whether accidental or intentional) is defined when a dosage higher than the recommended dosage is administered in one dose of study vaccine of Menveo®.

An overdose would also occur if two doses of the study vaccine are administered within half the time of the recommended interval between doses, as defined in the protocol.

Any vaccine administration error or overdose of study vaccine detailed in this protocol must be reported as an adverse event, and if the vaccine administration error or overdose is associated with a serious adverse event, it must be reported as such within 24 hours to the Sponsor.

6.5 Prior and Concomitant Medications and Vaccines

All medications, vaccines and blood products taken or received by the subject within 60 days prior to the start of the study are to be recorded on the Prior and Concomitant Medications and Blood Products CRF.

In addition, the following are considered prior medications for this protocol: all medication/vaccines described in the inclusion and exclusion criteria of this protocol including:

1. Subjects treated with systemic administration corticosteroids (PO/IV/IM) for more than 14 consecutive days from birth.
2. Subjects who received oral or parenteral antibiotic treatment in the 3 days prior to the scheduled blood draw

The use of antipyretics and/or analgesic medications within 24 hours prior to vaccination must be identified and the reason for their use (prophylaxis versus treatment) must be described in the source document and Concomitant Medications CRF.

Medications taken for prophylaxis are those intended to prevent the onset of symptoms. Medications taken for treatment are intended to reduce or eliminate the presence of symptoms that are present.

Concomitant medications taken-by/administered to the subject to treat any medically-attended AE and SAE and all vaccines at and after enrolment and must be documented on the Concomitant Medications /CRF.

When recording concomitant medications/vaccines, they should be checked against the study entry and continuation criteria in [section 4.0, Selection of Study Population](#) to ensure that the subject should be enrolled/continue in the study.

6.6 Vaccine Supply, Labeling, Storage and Tracking

The Sponsor will ensure the following:

- Supply the study vaccine(s).
- Appropriate labeling of all study provided that complies with the legal requirements of each country where the study is to be performed.

The investigator must ensure the following:

- Acknowledge receipt of the study vaccines by a designated staff member at the site, including:
 - Confirmation that the vaccines were received in good condition
 - Confirmation to the Sponsor of the temperature range during shipment from the Sponsor to the investigator's designated storage location
 - Confirmation by the Sponsor that the vaccines are authorized for use.
- Proper storage of the study vaccines, including:
 - Storage in a secure, locked, temperature-controlled location.
 - Proper storage according to the instructions specified on the labels.
 - Appropriate record keeping and inventory of the study vaccines, including regular documentation of adequate storage temperature.
- Appropriate use of the study vaccines, including:
 - Not use of vaccines prior to receipt of authorization for use from the Sponsor.
 - Use only in accordance with the approved protocol.
 - Proper handling, including confirmation that the vaccine has not expired prior to administration.
 - Appropriate documentation of administration of vaccines to study subjects including:
 - Date, dosage, batch/lot numbers, expiration dates, unique identifying numbers assigned to subjects and study vaccines, and time of vaccine administration. This information will be maintained in an accountability log that will be reviewed by the site monitor.
 - Reconciliation of all vaccines received from the Sponsor. Reconciliation is defined as maintaining records of which and how many vaccines were received, which vaccines were administered to subjects, which vaccines were destroyed at the site, and which vaccines were returned to the Sponsor, as applicable.
- Proper adherence to the local institutional policy with respect to destruction of study vaccines.
- Complete record keeping of vaccine use, wastage, return or destruction, including documentation of:
 - Copy of the site's procedure for destruction of hazardous material.

- Number of doses destroyed, date of destruction, destruction code (if available), method of destruction, and name of individual performing destruction.

Vaccines that have been stored differently from the manufacturer's indications **must not** be used unless the Sponsor provides written authorization for use. In the event that the use cannot be authorized, the Sponsor will make every effort to replace the vaccine supply. All vaccines used in conjunction with this protocol must be stored separately from normal hospital/practice stocks to prevent unintentional use of study vaccines outside of the clinical study setting.

Monitoring of vaccine accountability will be performed by the study monitor during site visits and at the completion of the study.

At the conclusion of the study, and as appropriate during the course of the study, the investigator must ensure that all unused study vaccines, packaging and supplementary labels are destroyed locally (upon approval from Sponsor) or returned to the Sponsor.

7.0 ASSESSMENTS

7.1 Safety Assessment

The measures of safety used in this study are based on comparable routine clinical procedures. They include a close vigilance for, and stringent reporting of, selected local and systemic adverse events routinely monitored in vaccine clinical studies as indicators of reactogenicity.

An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product at any dose that does not necessarily have to have a causal relationship with this treatment. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. This definition includes intercurrent illnesses or injuries and exacerbation of pre-existing conditions.

The period of observation for AEs extends from the time the subject's parent signs informed consent until the subject completes the specified safety follow-up period of approximately 12 months after the last study vaccination or terminates the study early (whichever comes first).

AEs occurring after the informed consent form is signed but prior to receiving study vaccine/product will be documented as an adverse event and recorded within source document. However, any AEs occurring prior to receipt of any study vaccine will be analyzed separately from "treatment emergent" AEs (AEs occurring after administration of the first study vaccine).

Adverse events are collected as either solicited or unsolicited adverse events. Solicited events are derived from organized data collection systems, such as Subject Diaries or interview.

7.1.1 Solicited Adverse Events

The term "reactogenicity" refers to solicited signs and symptoms ("solicited adverse events") occurring in the hours and days following a vaccination, to be collected by the subject parent(s)/legal guardian(s) for 7 consecutive days starting from the day of each study vaccination, using a pre-defined Subject Diary.

The following solicited adverse events are included in the Subject Diary. Each adverse event is to be assessed using the scoring system reported in parentheses below

Solicited Local Adverse Events

Injection site erythema, injection site induration, injection site tenderness.

Solicited local adverse events will be collected daily by the subject(s) parent(s)/legal guardian(s) for 7 consecutive days starting from the day of each study vaccination. They will be recorded in the Subject Diary and entered into the eCRF

Solicited Systemic Adverse Events

Change in eating habits, sleepiness, irritability, vomiting, diarrhea, fever. Fever is defined as body temperature $\geq 38.0^{\circ}\text{C}$ measured via tympanic route as preferred.

Solicited systemic adverse events will be collected daily by subject(s) parent(s)/legal guardian(s) for 7 consecutive days starting from the day of each study vaccination. They will be recorded in the Subject Diary and entered into the eCRF.

Other Solicited Adverse Events

- Use of analgesics / antipyretics for treatment (Days 1-7 after each study vaccination)
- Use of analgesics / antipyretics for prophylaxis (Days 1-7 after each study vaccination)
- Body temperature (preferably tympanic)

Above listed indicators of reactogenicity will be collected daily by the subject(s) parent(s)/legal guardian(s) for 7 consecutive days starting from the day of each study vaccination. They will be recorded in the Subject Diary and entered into the eCRF.

The study staff must review the data entered into the Subject Diary as described in [section 3.4.2, Tools Used for Data Collection](#) and [section 5.3.1, Follow-up Clinic Visit\(s\)](#).

Note: Any solicited adverse event that meets any of the following criteria must be entered into subjects' source document (see [section 9.1, Source Documentation](#)) and also as an adverse event on the Adverse Event CRF:

- Solicited local or systemic adverse event that continues beyond day 7 after vaccination.
- Solicited local or systemic adverse event that leads to a visit to a healthcare provider (medically attended adverse event, see [section 7.1.3, Evaluation of Adverse Events](#)).

- Solicited local or systemic adverse event leading to the subject withdrawing from the study or the subject being withdrawn from the study by the investigator (adverse event leading to withdrawal, see [section 7.1.3, Evaluation of Adverse Events](#)).
- Solicited local or systemic adverse event that otherwise meets the definition of a serious adverse event (see [section 7.1.4, Serious Adverse Events](#)).

7.1.2 Unsolicited Adverse Events

An unsolicited adverse event is an adverse event that was not solicited using a Subject Diary and that was spontaneously communicated by a subject parent(s)/legal guardian(s) who has signed the informed consent.

7.1.3 Evaluation of Adverse Events

Every effort should be made by the investigator to evaluate safety information reported by a subject for an underlying diagnosis and to capture this diagnosis as the event in the AE page. In other words, the practice of reporting only symptoms (e.g., “cough” or “ear pain”) are better reported according to the underlying cause (e.g., “asthma exacerbation” or “otitis media”).

The severity of events reported on the Adverse Events CRF will be determined by the investigator as:

Mild:	transient with no limitation in normal daily activity.
Moderate:	some limitation in normal daily activity.
Severe:	unable to perform normal daily activity.

The relationship of the study treatment to an AE will be determined by the investigator based on the following definitions:

1. Not Related

The AE is not related to an investigational vaccine if there is evidence that clearly indicates an alternative explanation. If the subject has not received the vaccine, the timing of the exposure to the vaccine and the onset of the AE are not reasonably related in time, or other facts, evidence or arguments exist that reasonably suggest an alternative explanation, then the AE is not related.

2. Possibly Related

The administration of the investigational vaccine and AE are considered reasonably related in time and the AE could be explained by exposure to the investigational vaccine or by other causes.

3. Probably Related

Exposure to the investigational vaccine and AE are reasonably related in time and no alternative explanation has been identified.

The relationship of the study treatment to an unsolicited AE will be determined by the investigator.

Note: solicited AEs will not be evaluated for relationship to study treatment. Grading for severity of solicited local and systemic AEs is described in [section 7.1.1, Solicited Adverse Events](#).

Adverse events will also be evaluated by the investigator for the co-existence of any of the other following conditions:

- “Medically attended adverse event”: an adverse event that leads to a visit to a healthcare provider.
- “New onset of chronic disease” (NOCD): an adverse event that represents a new diagnosis of a chronic medical condition that was not present or suspected in a subject prior to study enrolment.
- AEs leading to withdrawal: adverse events leading to study or vaccine withdrawal.

All AEs, regardless of severity, will be monitored until resolution or until the investigator assesses them as chronic or stable. All subjects experiencing AEs - whether considered associated with the use of the study vaccine or not - must be monitored until symptoms subside and any abnormal laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full pathologist’s report should be supplied, if possible. The investigator’s assessment of ongoing Adverse Events at the time of each subject’s last visit should be documented in the subject’s medical chart.

7.1.4 Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose results in one or more of the following:

- 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.
- Required or prolonged hospitalization.
- Persistent or significant disability/incapacity (i.e., the event causes a substantial disruption of a person's ability to conduct normal life functions).
- Congenital anomaly/or birth defect.
- 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 subject or may require intervention to prevent one of the other outcomes listed above.

Adverse events which do not fall into these categories are defined as non-serious.

It should be noted that a severe adverse event need not be serious in nature and that a serious adverse event need not, by definition, be severe.

Serious adverse events will be captured both on the Vaccines Serious Adverse Event (VSAE) form as well as on the AE CRF. All SAEs will be evaluated by the investigator for relationship of the event to study vaccine. SAEs that are judged to be possibly or probably related to the study vaccine should be reported to the Sponsor as related/suspected events.

The relationship of the study treatment to an SAE will be determined by the investigator based on the following definitions:

1. Related/suspected

The SAE is judged by the investigator to be possibly or probably related to the study vaccine on the AE CRF page (see [section 7.1.3, Evaluation of Adverse Events](#)).

2. Not Related

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

The relationship of the study vaccine to an SAE will be determined by the investigator.

In addition, SAEs will be evaluated by the Sponsor or designee for “expectedness.” An unexpected AE is one that is not listed in the current Summary of Product Characteristics or the Investigator’s Brochure or an event that is by nature more specific or more severe than a listed event.

In addition, a pre-existing event or condition that results in hospitalization should be recorded on the Medical History CRF. If the onset of an event occurred before the subject entered the study (e.g., any pre-planned hospitalization for conditions like cosmetic treatments or for non-emergency routine visits for a pre-existing condition), the hospitalization would not lead to an AE being classified as serious unless, in the view of the investigator, hospitalization was prolonged as a result of participation in the clinical study or was necessary due to a worsening of the pre-existing condition.

7.1.4.1 Adverse Events of Special Interest

Adverse events of special interest (AESIs) are not assessed during the study.

7.1.5 Methods for Recording Adverse Events and Serious Adverse Events

Findings regarding Adverse Events must be reported on an Adverse Events CRF, as specified in [section 7.1.1, Solicited Adverse Events](#), and on the VSAE form, if applicable, which is part of the Investigator Site File. All findings in subjects experiencing AEs must be reported also in the subject's source document.

All SAEs which occur during the course of the study, whether considered to be associated with the study vaccination or not, must be reported **within 24 hours of the site becoming aware of the event** to Novartis or its designee. Specific instructions and contact details for collecting and reporting SAEs to Novartis will be provided to the investigator.

All SAEs are also to be documented on the Adverse Events CRF. Any medication or other therapeutic measures used to treat the AE will be recorded on the appropriate CRF(s) in addition to the outcome of the AE.

After receipt of the initial report, representatives of Novartis or its designee will contact the investigator if it is necessary to obtain further information for assessment of the event.

All SAEs must be reported by the investigator to his/her corresponding EC or applicable regulatory authorities in accordance with institutional policy/regulatory requirements and adequate documentation of this notification must be provided to the Sponsor.

Novartis or its designee must also comply with the applicable regulatory requirement(s) related to the reporting of suspected unexpected serious adverse vaccine reactions (also

known as SUSARs) to the regulatory authority(ies) and the IRB/EC. If a SUSAR or other safety signal relating to use of one of the study vaccines is reported to Novartis or its designee, the Sponsor will communicate the information to the investigator and the investigator will be responsible for submitting this information to the EC /IRB and other relevant authorities.

7.1.5.1 Post-Study Events

Any suspected SAE that occurs outside of the protocol-specified follow-up period or after the end of the study but considered to be caused by the study vaccine must be reported to Novartis or its designee. These SAEs will be processed by Novartis or its designee as during the course of the study, until 3 months after last subject last visit. Instructions and contact details for collecting and reporting these suspected SAEs will be provided to the investigator.

7.1.6 Pregnancies

Not applicable for this study.

7.1.7 Safety Laboratory Measurements

Not applicable for this study.

7.2 Efficacy Assessment

There is no assessment of efficacy in this study.

7.3 Immunogenicity Assessment

The measures of immunogenicity used in this study are standard, i.e., widely used and generally recognized as reliable, accurate, and relevant (able to describe the quality and extent of the immune response).

The functional measure of immunogenicity used in this study, the serum bactericidal assay using complement (SBA), is a measure of the ability of antibodies, in concert with complement, to kill meningococci, and is widely used.

For the human SBA (hSBA) the complement is of human origin and generally recognized as the serological correlate of protection.

For the rabbit SBA (rSBA) the complement is derived from baby rabbits.

For the SBA analyses the serum samples of all subjects from visit 5 and visit 6 will be used.

The SBA will be used to measure the induction of functional bactericidal antibodies directed against the capsule polysaccharides of the meningococcal serogroups A, C, W and Y following study vaccination.

The measures of immunogenicity using this assay will be:

- hSBA: the percentages of subjects who achieve hSBA titers ≥ 8 and
- rSBA: the percentages of subjects who achieve titers ≥ 8 and ≥ 128 .
- hSBA and rSBA: GMT's.

Testing will be conducted by a Novartis or designated laboratory in a blinded manner towards the visit.

8.0 STATISTICAL CONSIDERATIONS

8.1 Endpoints

8.1.1 Primary Endpoint(s)

8.1.1.1 Primary Safety Endpoint(s)

Safety of the study vaccine will be assessed in all subjects in terms of the frequency and percentage of reported adverse events (AEs) including:

- Any solicited AEs reported within 30 minutes after each vaccination;
- Solicited local (i.e. erythema, induration and tenderness) and systemic (i.e. change in eating habits, sleepiness, irritability, vomiting, diarrhea, and fever (body temperature $\geq 38^{\circ}\text{C}$ (100.4°F)) AEs reported from Day 1 to Day 7 after each vaccination;
- All medically-attended unsolicited AEs reported from Day 1 to Visit 6 (24 months of age);
- AEs leading to premature withdrawal reported from Day 1 to Visit 6 (24 months of age);
- SAEs reported from Day 1 to Visit 6 (24 months of age);

8.1.1.2 Primary Efficacy Endpoint(s)

Not Applicable.

8.1.1.3 Primary Immunogenicity Endpoint(s)

One year after the full vaccination of 4 doses MenACWY (at 2 months, 4 months, 6 months and 12 months of age), establish the persistence by:

- Percentage of subjects with hSBA ≥ 8 for each serogroup.
- The percentage of subjects with rSBA ≥ 8 and with rSBA ≥ 128 for each serogroup.

8.1.2 Secondary Endpoint(s)

8.1.2.1 Secondary Safety Endpoint(s)

Not applicable

8.1.2.2 Secondary Efficacy Endpoint(s)

Not applicable

8.1.2.3 Secondary Immunogenicity Endpoint(s)

One month after the full vaccination of 4 doses MenACWY (at 2 months, 4 months, 6 months and 12 months of age), evaluate:

- Percentage of subjects with hSBA ≥ 8 for each serogroup
- The percentage of subjects with rSBA ≥ 8 and with rSBA ≥ 128 for each serogroup

One year after the full vaccination of 4 doses MenACWY (at 2 months, 4 months, 6 months and 12 months of age), establish the persistence by:

- hSBA GMT for each serogroup
- rSBA GMT for each serogroup

One month after the full vaccination of 4 doses MenACWY (at 2 months, 4 months, 6 months and 12 months of age), evaluate:

- hSBA GMT for each serogroup
- rSBA GMT for each serogroup

8.1.3 Exploratory Endpoint(s)

Not Applicable

8.1.3.1 Exploratory Safety Endpoint(s)

Not Applicable

8.1.3.2 Exploratory Efficacy Endpoint(s)

Not Applicable

8.1.3.3 Exploratory Immunogenicity Endpoint(s)

Not Applicable

8.2 Success Criteria

Not Applicable

8.2.1 Success Criteria for Primary Objective(s)

Not Applicable

8.2.1.1 Success Criteria for Primary Safety Objective(s)

Not Applicable

8.2.1.2 Success Criteria for Primary Efficacy Objective(s)

Not Applicable

8.2.1.3 Success Criteria for Primary Immunogenicity Objective(s)

Not Applicable

8.2.2 Success Criteria for Secondary Objective(s)

Not Applicable

8.2.2.1 Success Criteria for Secondary Safety Objective(s)

Not Applicable

8.2.2.2 Success Criteria for Secondary Efficacy Objective(s)

Not Applicable

8.2.2.3 Success Criteria for Secondary Immunogenicity Objective(s)

Not Applicable

8.3 Analysis Sets

8.3.1 All Enrolled Set

All screened subjects who provide informed consent and provide demographic and/or baseline screening assessments and received a Subject ID.

8.3.2 All Exposed Set

All subjects in the enrolled set who receive a study vaccination.

8.3.3 Safety Set

Solicited Safety Set (solicited local and systemic adverse events and other solicited adverse events)

All subjects in the Exposed Set with any solicited adverse event data and/or indicators of solicited adverse events

- Solicited Safety Set vaccination 1
All subjects in the Exposed Set with any solicited adverse event data and/or indicators of solicited adverse events from Day 1 of vaccination 1 and subsequent 6 days
- Solicited Safety Set vaccination 2
All subjects in the Exposed Set with any solicited adverse event data and/or indicators of solicited adverse events from Day of vaccination 2 and subsequent 6 days
- Solicited Safety Set vaccination 3
All subjects in the Exposed Set with any solicited adverse event data and/or indicators of solicited adverse events from Day of vaccination 3 and subsequent 6 days
- Solicited Safety Set vaccination 4
All subjects in the Exposed Set with any solicited adverse event data and/or indicators of solicited adverse events from Day of vaccination 4 and subsequent 6 days

Unsolicited Safety Set (unsolicited adverse events)

All subjects in the Exposed Set with unsolicited adverse event data.

Overall Safety Set

All subjects who are in any of the Solicited Safety Sets and/or Unsolicited Safety Set.

8.3.4 Full Analysis Set (FAS) Efficacy/Immunogenicity Set

Full Analysis Set Efficacy

Not Applicable

Full Analysis Set Immunogenicity

All subjects in the All Enrolled Set who, receive at least one study vaccination and provide in treatment immunogenicity.

- FAS hSBA 1 month
All subjects in the Exposed Set who provide evaluable hSBA immunogenicity data at 1 month after last vaccination
- FAS rSBA 1 month
All subjects in the Exposed Set who provide evaluable rSBA immunogenicity data at 1 month after last vaccination
- FAS hSBA 1 year
All subjects in the Exposed Set who provide evaluable hSBA immunogenicity data at 1 year after last vaccination
- FAS rSBA 1 year
All subjects in the Exposed Set who provide evaluable rSBA immunogenicity data at 1 year after last vaccination

8.3.5 Per Protocol (PP) Set Efficacy/Immunogenicity Set

All subjects in the different FAS populations Immunogenicity who:

- Have no protocol deviations leading to exclusion (see [section 8.3.8, Protocol Deviations](#)) as defined prior to analysis.

PPS are subsets of FAS and should be always defined even if the objectives do not require it. PPS sets will be named corresponding to the FAS populations, PPS hSBA 1 month, PPS rSBA 1 month, PPS hSBA 1 year and PPS rSBA 1 year.

An example for subjects excluded due to other reason than protocol deviations is when subjects withdrew informed consent.

8.3.6 Other Analysis Sets

Not Applicable

8.3.7 Subgroups

Not Applicable

8.3.8 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. A protocol deviation may be a reason to remove data from an analysis set at the time of analysis. CSR-reportable protocol deviations will be defined as exclusionary from the analysis according to protocol objectives and endpoints, which will be specified in the statistical analysis plan. In some cases exclusion of data may be due to a reason other than a protocol deviation, e.g. early termination.

8.4 Statistical Analysis Plan

8.4.1 Analysis of Demographic and Baseline Characteristics

Descriptive statistics (mean, standard deviation, median, minimum and maximum) for age, height and weight at enrolment will be calculated. Distributions of subjects by sex and ethnic origin will be summarized.

8.4.2 Analysis of Primary Objective(s)

8.4.2.1 Analysis of Primary Safety Objective(s)

8.4.2.1.1 Analysis of Extent of Exposure

The number of subjects actually receiving the vaccinations will be summarized.

8.4.2.1.2 Analysis of Solicited Local, Systemic and Other Adverse Events

Most solicited adverse events will be summarized according to defined severity grading scales.

Frequencies and percentages of subjects experiencing each adverse event will be presented for each symptom severity. Summary tables showing the occurrence of any local or systemic adverse event overall and at each time point will also be presented.

Post-vaccination solicited adverse events reported from 30 minutes, Day 1 to Day 3, Day 4 to Day 7 and Day 1 to Day 7 will be summarized by maximal severity.

The severity of solicited local adverse events, including injection site erythema, injection site induration, injection site tenderness will be categorized as none, 1 to ≤ 25 mm, 26 to ≤ 50 mm, and > 50 mm (severe local reactions).

Injection site pain/tenderness and systemic adverse events (except fever) occurring up to 7 days after each vaccination will be summarized according to “mild”, “moderate” or “severe”.

Each solicited local and systemic adverse event will also be further summarized as “none” versus “any”.

Implausible measurements (for further definition see statistical analysis plan) will be left out of the analysis.

Use of antipyretics and analgesics will be summarized by frequency by type of use (prophylactic versus treatment) and percentage of subjects reporting use. The influence of antipyretics and analgesics use on the occurrence of specific adverse events (e.g., fever, pain) will be assessed.

Body temperature will be categorized as $< 38^{\circ}\text{C}$ (no fever), $38-38.9^{\circ}\text{C}$ (Mild), $39-39.9^{\circ}\text{C}$ (Moderate), and $\geq 40^{\circ}\text{C}$ (severe). Body temperature will also be summarized by $< 38^{\circ}\text{C}$ (no fever), $38-38.4^{\circ}\text{C}$, $38.5-38.9^{\circ}\text{C}$, $39-39.4^{\circ}\text{C}$, $39.5-39.9^{\circ}\text{C}$, and $\geq 40^{\circ}\text{C}$ (severe).

8.4.2.1.3 Analysis of Unsolicited Adverse Events

This analysis applies to all adverse events occurring during the study, judged either as probably related, possibly related, or not related to vaccination by the investigator, recorded in AE CRF, with a start date on or after the date of first vaccination. AE starting prior to the first vaccination will only be listed. The original verbatim terms used by investigators to identify adverse events in the CRFs will be mapped to preferred terms using the MedDRA dictionary. The adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class.

All reported adverse events, as well as adverse events judged by the investigator as at least possibly related to study vaccine, will be summarized according to system organ class and preferred term within system organ class. These summaries will be presented by vaccination group and by interval of study observation. When an adverse event occurs more than once for a subject, the maximal severity and strongest relationship to the vaccine group will be counted.

Separate summaries will be produced for the following categories:

- Serious adverse events
- Adverse events that are possibly or probably related to vaccine
- Adverse event leading to withdrawal
- Adverse events leading to a medically attended visit

Data listings of all adverse events will be provided by subject. In addition, adverse events in the categories above will be provided as listed data.

8.4.2.1.4 Analysis of Safety Laboratory Values

Not Applicable

8.4.2.2 Analysis of Primary Efficacy Objective(s)

Not Applicable

8.4.2.2.1 Statistical Hypotheses

Not Applicable

8.4.2.2.2 Analysis Sets

Not Applicable

8.4.2.2.3 Statistical Methods

Not Applicable

8.4.2.3 Analysis of Primary Immunogenicity Objective(s)

8.4.2.3.1 Statistical Hypotheses

Not Applicable

8.4.2.3.2 Analysis Sets

The primary immunogenicity objective will be run with the FAS population, however the analyses will also be run with the PPS population for sensitivity reason.

8.4.2.3.3 Statistical Methods

Binary data

The primary objective of the study is the persistence one year after the complete schedule of 4 vaccinations, expressed as the number and percentage of subjects with hSBA titer ≥ 8 or rSBA titer ≥ 8 and ≥ 128 at Visit 6.

These percentages will be presented along with associated two-sided 95% Clopper-Pearson confidence intervals.

Handling of missing values for Immunogenicity Data

For immunogenicity data, it may be reasonable to consider missing immunogenicity values as missing completely at random, i.e. not informative. Therefore, the analysis will comprise a complete case analysis.

Titers below the limit of detection will be set to half that limit for the purposes of analysis.

8.4.3 Analysis of Secondary Objective(s)

8.4.3.1 Analysis of Secondary Safety Objective(s)

Not Applicable

8.4.3.1.1 Analysis of Extent of Exposure

Not Applicable

8.4.3.1.2 Analysis of Solicited Local, Systemic and Other Adverse Events

Not Applicable

8.4.3.1.3 Analysis of Unsolicited Adverse Events

Not Applicable

8.4.3.1.4 Statistical Hypotheses

Not Applicable

8.4.3.1.5 Analysis Sets

Not Applicable

8.4.3.1.6 Statistical Methods

Not Applicable

8.4.3.2 Analysis of Secondary Efficacy Objective(s)

8.4.3.2.1 Statistical Hypotheses

Not Applicable

8.4.3.2.2 Analysis Sets

Not Applicable

8.4.3.2.3 Statistical Methods

Not Applicable

8.4.3.3 Analysis of Secondary Immunogenicity Objective(s)

8.4.3.3.1 Statistical Hypotheses

Not Applicable

8.4.3.3.2 Analysis Sets

The analysis population will be the FAS defined in [Section 8.3](#). Immunogenicity analysis on the Per Protocol Population will also be performed for sensitivity.

8.4.3.3.3 Statistical Methods

Log-normal distributed data

The statistical analyses will be performed on the logarithmically (base 10) transformed values. Individual titers below detection limit will be set to half that limit.

Geometric mean antibody titers (GMT) and GMRs:

The antibody titers will be summarized using GMTs with two-sided 95% confidence intervals. The calculation will be done by an univariate analysis. GMTs and 95%

confidence intervals will be obtained by exponentiation (base 10) of the logarithmically transformed antibody titer and confidence limits. Moreover the geometric mean ratios (GMR) will be provided along with the 2-sided 95% confidence intervals. GMRs will be calculated between visit 6 (one year after full vaccination) and visit 5 (one month after full vaccination).

Median, minimum, and maximum values will be obtained using original titer values.

Binary data

The evaluation at one month after the complete schedule of 4 vaccinations is expressed as the number and percentage of subjects with hSBA titer ≥ 8 or rSBA titer ≥ 8 and ≥ 128 at Visit 5.

These percentages will be presented along with associated two-sided 95% Clopper-Pearson confidence intervals.

8.4.4 Analysis of Exploratory Objectives

Not Applicable

8.4.4.1 Analysis of Exploratory Safety Objective(s)

Not Applicable

8.4.4.2 Analysis of Exploratory Efficacy Objective(s)

Not Applicable

8.4.4.3 Analysis of Exploratory Immunogenicity Objective(s)

Not Applicable

8.5 Sample Size and Power Considerations of Primary and Secondary Objectives

Approximately 135 subjects will be enrolled in this study providing approximately 100 evaluable subjects, assuming a 25% drop-out. The sample size is based on the number of subjects requested and agreed with South Korean Health Authorities for this persistence study.

With 100 evaluable subjects, the 95% confidence limits of the observed percentages of subjects with hSBA titer ≥ 8 or rSBA titer ≥ 8 or ≥ 128 will be as presented in the following table.

Table 8.5-1: Calculated 95% Confidence Interval, Associated With Different Percentages of Observed Percentages of Subjects

Observed percentage	95% confidence interval (Menveo® N=100)
50%	40%- 60%
60%	50%-70%
70%	61%-79%
80%	72%-88%
90%	84%-96%

Dependent on the point estimate, the length of the confidence interval will be 12% - 20%.

8.6 Interim Analysis

No interim analysis of data from this study is planned.

9.0 SOURCE DOCUMENTATION, STUDY MONITORING AND AUDITING

In order to ensure consistency across sites, study monitoring and auditing will be standardized and performed in accordance with the Sponsor's or delegated contract research organization's (CRO) standard operating procedures and applicable regulatory requirements (e.g., FDA, EMA, and ICH guidelines).

Prior to enrolment of the first study subject, Novartis or delegate will train investigators and/or their study staff on the study protocol, all applicable study procedures, documentation practices and all electronic systems. CRFs supplied by the Sponsor must be completed for each enrolled subject (see [section 8.3.1, All Enrolled Set](#) for definition of enrolled subject). Documentation of screened but not enrolled subjects must be maintained at the site and made available for review by the site monitor. Data and documents will be checked by the Sponsor and/or monitor.

9.1 Source Documentation

Prior to the start of the study, the site staff participating in the study conduct will be instructed on what documents will be required for review as source documents. The kinds of documents that will serve as source documents will be agreed between Sponsor or delegate and investigator and designees and specified in the SDA prior to subject enrolment.

In addition, source documentation **must** include all of the following: subject identification (on each page), eligibility and participation, proper informed consent procedures, dates of visits, adherence to protocol procedures, adequate reporting and follow-up of adverse events, documentation of prior/concomitant medication/vaccines, study vaccine receipt/dispensing/return records, study vaccine administration information, any data collected by a telephone conversation with the subject parent(s)/legal guardian(s)] and date of completion and reason.

The subject parent(s)/legal guardian(s) must also allow access to the subject's medical records. Each subject parent(s)/legal guardian(s)] must be informed of this prior to the start of the study and consent for access to medical records may be required in accordance with local regulations.

All safety data reported by subjects must be written down in source documents prior to entry of the data into CRFs. If there are multiple sources of information (e.g., Subject Diary, verbal report of the subject, telephone contact details, medical chart) supporting the diagnosis of an adverse event, these sources must be identified in the source documents, discrepancies between sources clarified, the ultimate diagnosis must be

justified and written in the source documents, and this diagnosis must be captured in the Adverse Event CRF (AE CRF). The AE CRF must also capture which source(s) of information were used to determine the adverse event (e.g., subject recall, medical chart, Subject Diary).

9.2 Study Monitoring, Auditing and Source Data Verification

Prior to enrolment of the first study subject, Novartis or its designee (e.g., a CRO) will develop a Clinical Monitoring Plan to specify how centralized and/or on-site monitoring, including clinical specimens reconciliation, will be performed for the study. Study progress will be monitored by Novartis or its designee as frequently as necessary to ensure:

- that the rights and well-being of human subjects are protected,
- the reported study data are accurate, complete, and verifiable from the source documents and
- the conduct of the study is in compliance with the current approved protocol/amendment(s), GCP and applicable regulatory requirements.

Contact details for the Novartis team or its designee involved in study monitoring will be provided to the investigator. Study data recorded on CRFs will be verified by checking the CRF entries against source documents in order to ensure data completeness and accuracy as required by study protocol except for those parameters which are specifically described in [section 7.0, Assessment](#) being entered directly into the EDC system.

Data verification may also be performed through a centralized review of data (e.g., checking for outliers or other anomalies). Additional documents such as the investigator site file, pharmacy records, and informed consent documentation must also be available for review if requested. Arrangements for monitoring visits will be made in advance in accordance with the monitoring plan, except in case of emergency.

The investigator and/or site staff must make source documents of subjects enrolled in this study available for inspection by Novartis or its representative at the time of each monitoring visit and Sponsor audits, when applicable. These documents must also be available for inspection, verification and copying, as required by regulations, by officials of the regulatory health authorities (e.g., FDA, EMA and others) and/or ECs/IRBs. The investigator and study site staff must comply with applicable privacy, data protection and medical confidentiality laws for use and disclosure of information related to the study and enrolled subjects.

10.0 DATA MANAGEMENT

10.1 Data Entry and Management

In this study, all clinical data (including, but not limited to, AE/SAEs, concomitant medications, medical history, and physical assessments), safety data, and immunogenicity data will be entered onto case report forms (CRFs) in a timely fashion by the investigator and/or the investigator's dedicated site staff. Data entered onto CRFs are stored on a secure website. The data collected on this secure website are assimilated into an electronic data capture (EDC) system, which is compliant with Title 21 Part 11 policies of the Code of Federal Regulations ([FDA 1997](#)). The data system includes password protection and internal quality checks. The EDC system will be designed and validated by the Sponsor prior to activation for data entry by sites. The investigator or designated delegate must review data entered and electronically sign the CRFs to verify their accuracy.

Access to the EDC system for data entry or review will require training and distinct individual access code assignments to those site staff members who will be entering study data and those involved in study oversight who may review study data. Data are collected within the EDC system, to which the Sponsor and site monitors have exclusively "read only" access.

10.2 Data Clarification

As part of the conduct of the trial, the Sponsor may have questions about the data entered by the site, referred to as queries. The monitors and the Sponsor are the only parties that can generate a query. All corrections and clarifications will be entered into the EDC system and will be identified by the person entering the information, the reason for the change, as well as the time of the changes made. If changes are made to a previously and electronically signed CRF, the investigator must confirm and endorse the changes.

10.3 Data Protection

Novartis respects the subjects' rights to privacy and will ensure the confidentiality of their medical information in accordance with all applicable laws and regulations.

11.0 RECORD RETENTION

Investigators must retain all study records required by Novartis and by the applicable regulations in a secure and safe facility. The investigator must consult a Novartis representative before disposal of any study records, and must notify the Sponsor of any change in the location, disposition, or custody of the study files. Essential documents must be retained for 15 years. “Essential documents” are defined as documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced. These documents should be retained for a longer period, however, if required by the applicable national regulatory or institutional requirements.

These principles of record retention will also be applied to the storage of laboratory samples, provided that the integrity of the stored sample permits testing.

12.0 USE OF INFORMATION AND PUBLICATION

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov, and in compliance with current regulations.

Novartis also assures that key results of this clinical study will be posted in a publicly accessible database within the required time-frame from the end of study as defined in [section 3.9, End of Study](#).

In accordance with standard editorial, ethical practices and current guidelines of Good Publication Practice ([Graf 2009](#)), Novartis will generally support publication of multicenter studies only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement prior to the start of the study. The coordinating investigator will also sign the clinical study report on behalf of the principal investigators ([CPMP/EWP/2747/00](#)). Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Novartis personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Novartis personnel.

Novartis must be notified of any intent to publish data collected from the study and prior approval from Novartis must be obtained prior to submission for publication.

13.0 ETHICAL CONSIDERATIONS

13.1 Regulatory and Ethical Compliance

The study will be conducted in compliance with the protocol, GCP and applicable regulatory requirement(s).

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including [European Directive 2001/20/EC](#), [US Code of Federal Regulations Title 21](#), and [Japanese Ministry of Health, Labor, and Welfare](#)), Novartis codes on protection of human rights, and with the ethical principles laid down in the Declaration of Helsinki ([European Council 2001](#), [US Code of Federal Regulations](#), [ICH 1997](#));(59th World Medical Association General Assembly (October 2008)

13.2 Informed Consent Procedures

Eligible subjects may only be included in the study after providing written informed consent or assent, as described in [section 5.1.1, Informed Consent/Assent](#). Before the start of the study, the investigator will have the informed consent and any other materials that will be provided to the subjects reviewed and approved by the IRB/EC. This review and approval will be documented and stored with other study documents. The investigator or designee must fully inform the subject or legal guardian of all pertinent aspects of the study. A copy of the written informed consent will be given to the subject or the designee. The subject/designee must be allowed ample time to ask about the details of the study and to make a decision as to whether or not to participate in the study. The subject and/or legal guardian(s) **must** sign the consent form indicating their agreement to participate in the study before any study-related procedures are conducted. The informed consent process may be conducted up to 5 days prior to vaccination on day 1. If the subject and/or legal guardian(s) is unable to read and write, a witness must be present during the informed consent discussion and at the time of informed consent signature.

Prior to the start of the study, Novartis will provide to investigators a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/EC and a copy of the approved version must be provided to the Novartis monitor after IRB/EC approval.

In addition, the investigator or designee should explain pertinent aspects of the study in an age appropriate manner to pediatric subjects who are eligible for informed assent in accordance with local policies. The parent(s)/legal guardian(s) must be allowed ample

time to ask about the details of the study and to make a decision as to whether or not to participate in the study. The parent(s)/legal guardian(s)] must sign the consent/assent forms indicating their agreement to participate in the study before any study-related procedures are conducted. If the parent(s)/legal guardian(s)] are unable to read and write, a witness must be present during the informed consent/assent discussion and at the time of informed consent/assent signature.

13.3 Responsibilities of the Investigator and IRB/EC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted IRB/EC before study start. Properly constituted IRB/EC is defined in ICH Guideline for Good Clinical Practice E6 (R1), Section 3 (ICH 1997). A signed and dated statement that the protocol and informed consent have been approved by the IRB/EC must be given to Novartis before study initiation. Prior to study start and at any time the protocol is amended during study conduct, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/ECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

The investigator also responsible for the following:

- Maintaining a list of appropriately qualified persons to whom the investigator has delegated significant study-related duties
- Demonstrating the capability of recruiting the required number of suitable subjects within the recruitment period
- Demonstrating sufficient time and staffing to properly conduct and complete the study within the agreed study period
- Ensuring that all persons assisting with the study are adequately informed about the protocol, the investigational product(s), and their study-related duties and functions
- Ensuring that appropriately trained health care professionals are responsible for all study-related medical decisions and for ensuring appropriate medical care of subjects experiencing any adverse event related to the study
- If permission to do so is given by the subject parent(s)/legal guardian(s)], ensuring that the subject's primary healthcare provider is informed of the subject's participation in the study

The investigator should not implement any deviation from, or changes of the protocol without agreement by the Sponsor and prior review and documented approval/favourable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor(s), change of telephone number(s)). In addition, the investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to study subjects without prior IRB/IEC approval/favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

- (a) to the IRB/IEC for review and approval/favourable opinion,
- (b) to the Sponsor for agreement and, if required,
- (c) to the regulatory authority(ies).

13.4 Protocol Amendments

An amendment is a written description of change(s) to or formal clarification of a study protocol which may impact on the conduct of the clinical study, potential benefit of the clinical study, or may affect subject safety, including changes of study objectives, study design, subject population, sample sizes, study procedures, or significant administrative aspects. An administrative change of a study protocol is a minor correction or clarification that has no significant impact on the way the clinical study is to be conducted and no effect on subject safety (e.g., change of telephone number(s), logistical changes). Protocol amendments must be approved by Novartis, health authorities where required, and the IRB/EC. In cases when the amendment is required in order to protect the subject safety, the amendment can be implemented prior to IRB/EC approval. Notwithstanding, the need for formal approval of a protocol amendment, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action, the IRB/EC at the study site, and, if required by local regulations, the relevant health authority) should be informed within 10 working days.

14.0 REFERENCE LIST

1. Goldschneider I, Gotschlich EC, Artenstein MS. (1969) Human immunity to the meningococcus. I. The role of humoral antibodies. J Exp Med; 129: 1307-1326.
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4. ICH (1998) ICH Harmonised Tripartite ICH Guideline for Statistical Principles for Clinical Trials E9. Federal Register, 63 (179): 49583
5. 59th World Medical Association General Assembly (October 2008) Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. Seoul, Korea
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7. Rouphael NG and Stephens DS. *Neisseria meningitidis*: Biology, Microbiology, and Epidemiology. Methods Mol Biol. 2012;799:1-20.
8. Al-Tawfiq JA, Clark TA and Memish ZA. Meningococcal disease: the organism, clinical presentation, and worldwide epidemiology. J Travel Med 2010; 17 Suppl:3-8.
9. Deasy A and Read RC. Challenges for development of meningococcal vaccines in infants and children. Expert Rev. Vaccines 2011; 10: 335–343.

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Document Approval Certificate / PPD

The individuals listed have approved this document for implementation using an electronic signature in the Atlas EDMS. PPD

UserName: PPD

Title: Cluster Physician

Date: Thursday, 11 December 2014, 14:57 GMT

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PPD

CLINICAL STUDY PROTOCOL V59_75

A Phase IV, Open-Label, Multi-Center Study to Evaluate the Safety and the 1-year Persistence of Antibody Response Among Children Who Received 4 Doses of the GSK MenACWY Conjugate Vaccine at 2, 4, 6 and 12 Months of Age in South Korea

Amendment Number 1

Revised Protocol version 2.0 issued on 25 August 2015

The present amendment reflects changes to the Protocol version 1.0

Issued on 10 Dec 14

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DESCRIPTION OF CHANGE(S) AND RATIONALE:

CHANGE 1

The entire document has been revised to ensure all instances where Novartis is mentioned are replaced with GSK.

Rationale for Change:

Due to change of Marketing Authorization Holder from Novartis Vaccines to GSK Vaccines, the protocol has been revised to change name of Sponsor.

Novartis

Document Approval Certificate / PPD

The individuals listed have approved this document for implementation using an electronic signature in the Atlas EDMS. PPD

UserName: PPD

Title: Cluster Physician

Date: Wednesday, 02 September 2015, 11:31 GMT

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PPD

CLINICAL STUDY PROTOCOL AMENDMENT

Study Number: V59_75

Protocol Title: A Phase IV, Open-Label, Multi-Center Study to Evaluate the Safety and the 1-year Persistence of Antibody Response Among Children Who Received 4 Doses of the GSK MenACWY Conjugate Vaccine at 2, 4, 6 and 12 Months of Age in South Korea

Amendment Number 2

Revised Protocol version 3 issued on 26 Feb 2016

The present amendment reflects changes to the Revised Protocol version 2.0 issued on 25 AUG 15

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DESCRIPTION OF CHANGE(S) AND RATIONALE:

The present Clinical Study protocol Amendment is considered non-substantial and it is being issued to update the range of age of Menveo indication in the countries mentioned in the synopsis.

In addition, this amendment aimed to better clarify the visit window in time and events table. The visit interval between V3~V4 and V5~V6 were not clear on the current protocol. It was added a row called 'days post injection' to avoid confusion between INVs.

Finally, some changes were implemented to correct minor inconsistencies detected in Section # of the Clinical Study Protocol.

CHANGE 1 (*Page 9, 23 Background and rationale*):

Previously read:

GSK MenACWY Menveo[®] has been approved for use in people 2 months through 55 years of age in the United State and in people 2 years up to 55 in Europe and other countries, including the Republic of South Korea.

Now reads:

GSK MenACWY Menveo[®] has been approved for use in people 2 months through 55 years of age in the United States and in children (from 2 years of age), adolescents and adults in Europe.

Rationale for Change:

In Europe Menveo is indicated for use in people from 2 years of age without upper age limit.

CHANGE 2 (*Page 12, Paragraph: Study Procedures*):

Previously read:

Visit 2 (Age 4 Months) (60 days after Visit 1 +/- 7 days). At Day 3 after vaccination a telephone call will be made to remind the subjects' parents/legal guardian to complete the subject diary.

Now reads:

At study Day 63 (2 days after the 2nd vaccination) after vaccination a telephone call will be made to remind the subjects' parents/legal guardian to complete the subject diary.

Rationale for Change and Changes #3, #4 and #5 below:

The visit intervals between V3 to V4 and V5 to V6 were incorrect and caused confusion between investigators. Intervals are now described as study days after the relevant vaccination for clarity.

CHANGE 3 (*Page 13, Paragraph: Study Procedures*):

Previously read:

Visit 3 (Age 6 months) (60 days after Visit 2 +/- 7 days). At Day 3 after vaccination a telephone call will be made to remind the subjects' parents/legal guardian to complete the subject diary.

Now reads:

At study Day 123 (2 days after the 3rd vaccination) after vaccination a telephone call will be made to remind the subjects' parents/legal guardian to complete the subject diary.

Rationale for Change:

Text added for clarification.

CHANGE 4 (*Page 13, Paragraph: Study Procedures*):

Previously read:

Visit 4 (Age 12 Months) (Inclusive + 14 days). At Day 3 after vaccination a telephone call will be made to remind the subjects' parents/legal guardian to complete the subject diary.

Now reads:

At study day 303 (2 days after the 4th vaccination) after vaccination a telephone call will be made to remind the subjects' parents/legal guardian to complete the subject diary.

Rationale for Change:

Text added for clarification.

CHANGE 5 (Page 18, Time and Events Table – Treatment Period):

Previously read:

Changes highlighted in yellow.

Visit Type	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Clinic Visit	Clinic Visit
Study Day	1	3	61	63	121	123	301	304	331	661

Now reads:

Visit Type	Clinic Visit	Reminder Phone Call	Clinic Visit	Reminder Phone Call	Clinic Visit	Reminder Phone Call	Clinic Visit	Reminder Phone Call	Clinic Visit	Clinic Visit
Study Day	1	3	61	63	121	123	301	303	331	661
Days Post Injections		2 days post dose 1	60 days post dose 1	2 days post dose 2	60 days post dose 2	2 days post dose 3	180 days post dose 3	2 days post dose 4	30 days post dose 4	330 days post visit 5

Rationale for Change # 5:

A new row titled ‘Days Post injections’ has been inserted to align with text above and to better clarify the intervals between visits and the reminder call.

CHANGE 6 (Page 33, 45; Section Exclusion Criteria, Prior and Concomitant Medication and Vaccines):

Previously Read:

Received oral or parenteral antibiotic treatment in the 3 days prior to the scheduled blood draw (topical antibiotics are acceptable, including antibiotic eye drops).

Now Reads:

Received oral or parenteral antibiotic treatment in the 7 days prior to the scheduled blood draw (topical antibiotics are acceptable, including antibiotic eye drops).

Rationale for Change # 6:

The # of days of delay in case of antibiotics treatment was incorrectly recorded as 3 instead of 7 days.

CHANGE 7 (Page 33, Section 4.3):

Previously Read:

NA

Now Reads:

There are clinical circumstances that warrant delay of blood collection for immunogenicity assessments in this study. These situations are listed below. In the event that a subject meets a criterion for delay of blood collection, blood collection may proceed once the window for delay has passed.

Subject has received oral or parenteral antibiotic treatment in the 7 days prior to the scheduled blood draw (topical antibiotics are acceptable, including antibiotic eye drops).

Rationale for Change # 7:

To provide further clarification on criteria for delay in blood draw, aligned with Change 6 above.

CHANGE 8 (*Page 45, Section 6.5*):

Previously Read:

All medications, vaccines and blood products taken or received by the subject within 60 days prior to the start of the study are to be recorded on the Prior and Concomitant Medications and Blood Products CRF

Now Reads:

All medications, vaccines and blood products taken or received by the subject since birth are to be recorded on the Prior and Concomitant Medications and Blood Products CRF.

Rationale for Change # 8:

To be aligned with the protocol synopsis.

CHANGE 9 (*Page 62, Section 8.4.2.1.2*):

Previously Read:

The severity of solicited local adverse events, including injection site erythema, injection site induration, injection site tenderness will be categorized as none, 1 to ≤ 25 mm, 26 to ≤ 50 mm, and > 50 mm (severe local reactions).

Now Reads:

The severity of solicited local adverse events, including injection site erythema and, injection site induration, were summarized according to categories based on linear measurement: 1-9 mm ('none'), 10 to 25 mm ("mild"), 26 to 50 mm ("moderate"), and > 50 mm ("severe").

Rationale for Change # 9:

Injection site tenderness is not classified in terms of size and has been deleted. Classification of injection site tenderness is already specified in the next paragraph of the protocol.

In addition, the ranges for classification of erythema and site induration were updated in conformance with the classification used in the latest toddler study for Menveo V59_67.

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PPD

The individuals listed have approved this document for implementation using an electronic signature in the Atlas EDMS. / PPD

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