A Multicenter Post Marketing Surveillance Study to Monitor the Safety of Novartis Meningococcal ACWY Conjugate Vaccine (MenACWY-CRM) Administered According to the Prescribing Information to Healthy Subjects from 11 to 55 Years of Age in the Republic of South Korea

CLINICAL STUDY PROTOCOL V59_62

PROTOCOL SYNOPSIS V59_62

Name of Sponsor Novartis Vaccines and Diagnostics	**Protocol number:** V59_62		**Date of Protocol Synopsis:** 22 NOV 11

Title of Study: A Multicenter Post Marketing Surveillance Study to Monitor the Safety of Novartis Meningococcal ACWY Conjugate Vaccine (MenACWY-CRM) Administered According to the Prescribing Information to Healthy Subjects from 11 to 55 Years of Age in the Republic of South Korea.

Publication (reference): None

Study Period: 29 days	Clinical Phase: Post Marketing Surveillance

Rationale:

Neisseria meningitidis is a leading cause of bacterial meningitis and sepsis with a fatality rate of 5% to 15%; the fatality rate can be as high as 20% to 40% in meningococcal septicemia.

In Korea meningococcal disease is a notifiable disease and any confirmed case is reported to the Korea Centers for Disease Control and Prevention. The disease has been regarded as a rare infection. However, during the period from 2002 to 2003 the number of reported cases in Korea dramatically increased, suggesting that the burden of meningococcal disease should be taken in serious consideration in this Country.

Limited data are available about the incidence of meningococcal disease among age groups in Korea. Military personnel are considered to have a higher risk for the disease, probably due to the crowded living conditions. A specific group that has several characteristics in common with the military personnel is college students, especially dormitory residents. Nevertheless, one report, aiming to the serological characterization of 11 meningococcal isolates in Korea, shows an even distribution of cases among age groups (0-5 years: 2 subjects; 6-10 years: 2 subjects; 11-17 years: 2 subjects; 18-30 years: 2 subjects; 31-55: 2 subjects; >56 years: 1 subject).

Novartis Vaccines and Diagnostics (NVD) has developed a conjugate meningococcal ACWY (MenACWY-CRM) vaccine containing bacterial capsular oligosaccharides for serogroups A, C, W, and Y conjugated to a protein carrier CRM_{197} (a non-toxic mutant of diphtheria toxin). MenACWY-CRM is currently licensed in many Countries including Korea. Over 35,000 subjects have been enrolled in more than 30 clinical studies with over 25,000 receiving at least one dose of MenACWY-CRM.

This is a post-marketing surveillance study to monitor the safety of MenACWY-CRM in Korean individuals from 11 to 55 years of age receiving MenACWY-CRM vaccination according to routine clinical practice and prescribing information. The study

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is a post-licensure requirement of the Korea Food and Drug Administration (KFDA) to provide continued safety evaluation in the Korean population from 11 to 55 years of age.

Study Agent:

MenACWY-CRM Conjugate Vaccine (Menveo), one 0.5 mL dose to be administered by intramuscular injection in the deltoid area of (preferably) the non-dominant arm.

Objectives:

Immunogenicity and efficacy objectives

No immunogenicity or efficacy objectives will be measured in this study.

Safety objectives

The primary objective of the study is to monitor the safety of a single dose of MenACWY-CRM vaccine in subjects from 11 to 55 years of age , as evaluated by:

- Local and systemic solicited reactions reported from study Day 1 (day of vaccination) through study Day 7 post-vaccination;
- All unsolicited adverse events (AEs) reported from study Day 1 (day of vaccination) through study Day 7 post-vaccination;
- Medically attended adverse events reported from study Day 1 to study termination (Day 29/early termination);
- All Serious adverse events (SAEs) reported from study Day 1 to study termination (Day 29/early termination).

Methodology:

This is a multicenter post marketing surveillance study to monitor the safety of MenACWY-CRM (Menveo) administered according to the prescribing information to 3,300 healthy subjects from 11 to 55 years of age in Korea.

Visit No.		**1**	☎/✉
Age (years)	**# of Subjects**	**Day 1**	**Day 29 (-4/+7 days)**
11-55 years	3,300	Menveo	Safety

Subjects will be enrolled at the time of their visit to a participating clinic or hospital for vaccination with MenACWY-CRM according to routine clinical practice.

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At Visit 1 (Day 1) the informed consent will be obtained from the subjects or subject's parent/legal representative. The vaccination will be administered. Subjects will remain under observation for at least 30 minutes in the clinic after study immunization; during this period subjects will be evaluated for any immediate hypersensitivity reactions and other adverse events.

The subjects or subject's parent/legal representative will then be instructed to complete the Diary Card daily for 7 days, reporting local and systemic reactions and all AEs occurring within 7 days following immunization, and all medically attended AEs and SAEs occurring up to Day 29.

Subjects will also be instructed to return the completed diaries to the study site at Day 29 as follows:

- During a visit at the study center or
- Using the provided pre-addressed stamped envelope (PASE).

At the discretion of the investigator, the subject or subject's parent/legal representative will be reminded of the date of the study termination by a phone call at Day 29. If any clarification is required after Diary Card retrieval the site staff will follow up by phone, and any additional finding will be recorded on the subject's medical record.

In case the Diary Card is not retrieved within 10 days after Day 29, subject or subject's parent/legal representative will be contacted by phone to assess the occurrence of adverse events, determine the subject's clinical status and complete study termination. All information will be recorded by the site staff on the subject's medical record and collected in the appropriate section of the CRF.

All 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 NVD medical monitor to determine whether continued follow up of the SAE is needed.

Safety Assessment Table

The following table summarizes relevant safety assessments:

Medical History: All significant past diagnoses including all allergies, major surgeries requiring inpatient hospitalization, other significant injuries or hospitalizations, any conditions requiring prescription or chronic medication (i.e., >2 weeks in duration), or other significant medical conditions based on the investigator's	From birth, collected at clinic Visit Day 1

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judgment.	
Immediate reactions: Subjects will be assessed for immediate hypersensitivity reactions.	For at least 30 minutes after vaccination
Local reactions: Erythema, induration, pain.	Days 1-7 after vaccination
Systemic reactions: Chills, nausea, malaise, myalgia, arthralgia, headache, rash, fever.	Days 1-7 after vaccination
All unsolicited AEs will be collected	Days 1-7 after vaccination
Medically attended Adverse Events: Events that require a physician's visit or an emergency room visit (*events that are managed by telephone or means other than a face-to-face evaluation by a clinician do not qualify as medically attended AEs*).	From Day 1 to study termination (Day 29/early termination)
Serious AEs: All SAEs will be collected.	From Day 1 to study termination (Day 29/early termination)
Medications: Any medications used to treat any solicited local and systemic reaction and unsolicited AE be collected.	From Day 1 to Day 7
Medications: Any medications used to treat any medically attended AE or SAE will be collected.	From Day 1 to study termination (Day 29/early termination)

Number of Subjects Planned:

A total of approximately 3,300 subjects are planned for enrolment into this study, within a 6 years period. Assuming a 10% drop-out rate, this should provide approximately 3,000 evaluable subjects, in compliance with KFDA requirements.

Clinics and hospitals including pediatricians and family doctors will be involved in the study.

Subject Population:
Healthy male and female subjects from 11 to 55 years of age will be enrolled. They will be identified among subjects attending to participating clinics or hospitals for vaccination with MenACWY-CRM according to routine clinical practice.

Subject Characteristics and Main Criteria for Inclusion and Exclusion:
A detailed list of criteria is included in protocol section 4.0
Inclusion criteria: Male and female subjects, of from 11 to 55 years of age (including

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all 55 years old subjects, up to one day before their 56th year birthday), who are scheduled to receive MenACWY-CRM conjugate vaccine according to the Korean prescribing information, who or whose legally acceptable representative have given written informed consent at the time of enrollment, and who are able to comply with all study procedure.
Exclusion criteria: Contraindication, special warnings and/or precautions, as evaluated by the investigators, reported in the MenACWY-CRM conjugate vaccine Korean prescribing information.

Vaccines:
MenACWY-CRM conjugate vaccine (Menveo).
The vaccine will not be provided by the sponsor. Commercial supplies used in routine clinical practice will be utilized in this study.
There is no placebo or test vaccine being evaluated in this study.

Safety Endpoints:
Safety will be assessed after administration of study vaccine in terms of the number and percentage of subjects with:

- Local and systemic solicited reactions reported from study Day 1 (day of vaccination) through study Day 7 post-vaccination;
- Unsolicited AEs reported from study Day 1 (day of vaccination) through study Day 7 post-vaccination;
- Medically attended AEs reported from study Day 1 to study termination (Day 29/early termination);
- SAEs reported from study Day 1 to study termination (Day 29/early termination).

Statistical Considerations:

All analyses will be run descriptively; no statistical (null) hypothesis is associated with the primary safety objective.

A total of approximately 3,300 subjects are planned for enrolment into this study. Assuming a 10% drop-out rate, this should provide approximately 3,000 evaluable subjects. This sample size meets the post-licensure requirements of the KFDA to provide continued safety monitoring in the Korean population.

Interim Analysis:

NVD will provide biannual (every 6 months) study status reports during the first two years, and annual reports from the third to the sixth year, in compliance with KFDA requirements.

Data Monitoring Committee: No Data Monitoring Committee will be convened for this study.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

AE	Adverse Event
CRF	Case Report Form
CRO	Contract Research Organization
DCF	Data Clarification Form
EC	Ethics Committee
EP	European Pharmacopea
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICD	International Classification of Diseases
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IM	Intramuscular
IRB	Institutional Review Board
KFDA	Korean Food and Drug Administration
MedDRA	Medical Dictionary for Regulatory Activities
NCR	No carbon required
NVD	Novartis Vaccines and Diagnostics
PMS	Post Marketing Surveillance
SAE	Serious Adverse Event
PASE	Pre Addressed Stamped Envelope
VSAE	Vaccine Serious Adverse Event
WHO	World Health Organization

1.0 BACKGROUND AND RATIONALE

Neisseria meningitidis is a leading cause of bacterial meningitis and sepsis with a fatality rate of 5% to 15%; the fatality rate can be as high as 20% to 40% in meningococcal septicemia [Rouphael and Stephens 2012, Al-Tawfiq et al 2010, Hill et al 2010, Deasy and Read 2011]. In addition, 12% to 19% of survivors develop long-term neurologic sequelae [Al-Tawfiq et al 2010]. Most cases of *N. meningitidis* infection are caused by close contact with carriers of the infectious agent, with nearly 15% of adolescents [Al-Tawfiq et al 2010] and 10%-35% of adults [Hill et al 2010] acting as carriers. Young children are at the highest risk for invasive disease, with peaks in incidence in children under 4 years and young adults 15-19 years [Deasy and Read 2011].

In Korea meningococcal disease is a notifiable disease and any confirmed case is reported to the Korea Centers for Disease Control and Prevention [Song-Mee and Yeon-Ho 2008]. The disease has been regarded as a rare infection [Song-Mee and Yeon-Ho 2008]. However, during the period from 2002 to 2003 the number of reported cases in Korea dramatically increased [Korea Center for Disease Control and Prevention 2007], suggesting that the burden of meningococcal disease may be significant in this Country.

Limited data are available about the incidence of meningococcal disease among age groups in Korea. In retrospective surveys of several hospitals in Korea from 1996 to 2005, *N. meningitidis* accounted for 24% to 37% of bacterial meningitis cases in children aged over 5 years, with a case fatality rate of 15% to 26% [Lee et al 2011, Cho et al 2011]. Another survey of adults with community-acquired bacterial meningitis reported that *N. meningitidis* was the causative organism in 2.6% of cases from 1998 to 2008 in Korea [Moon et al 2010]. Military personnel are considered to have a higher risk for the disease, probably due to the crowded living conditions [Al-Tawfiq et al 2010]. A specific group that has several characteristics in common with the military personnel is college students, especially dormitory residents. Nevertheless, one report, aiming to the serological characterization of 11 meningococcal isolates in Korea, shows an even distribution of cases among age groups (0-5 years: 2/11 subjects; 6-10 years: 2/11 subjects; 11-17 years: 2/11 subjects; 18-30 years: 2/11 subjects; 31-55: 2/11 subjects; >56 years: 1/11 subject) [Song-Mee and Yeon-Ho 2008].

Novartis Vaccines and Diagnostics (NVD) has developed a conjugate meningococcal ACWY (MenACWY-CRM) vaccine [Trotter et al 2004, Obaro et al 2006] containing bacterial capsular oligosaccharides for serogroups A, C, W, and Y conjugated to a protein carrier CRM_{197} (a non-toxic mutant of diphtheria toxin). MenACWY-CRM is currently licensed in many countries including Korea. Over 35,000 subjects have been enrolled in more than 30 clinical studies with over 25,000 receiving at least one dose of MenACWY-CRM.

This is a post-marketing surveillance (PMS) study to monitor the safety of MenACWY-CRM in Korean individuals from 11 to 55 years of age receiving MenACWY-CRM

vaccination according to routine clinical practice and prescribing information. The study is a post-licensure requirement of the Korea Food and Drug Administration (KFDA) to provide continued safety evaluation in the Korean population. The post-marketing surveillance study will be performed in accordance with the principles outlined by KFDA.

2.0 OBJECTIVES

Immunogenicity Objectives:

No immunogenicity or efficacy objectives will be measured in this study.

Safety objectives:

The primary objective of the study is to monitor the safety of a single dose of MenACWY-CRM vaccine in subjects from 11 to 55 years of age, as evaluated by:

- Local and systemic solicited reactions reported from study Day 1 (day of vaccination) through study Day 7 post-vaccination;
- All unsolicited Adverse Events (AEs) reported from study Day 1 (day of vaccination) through study Day 7 post-vaccination;
- Medically attended Adverse Events reported from study Day 1 to study termination (Day 29/early termination).
- All Serious Adverse Events (SAEs) reported from study Day 1 to study termination (Day 29/early termination).

3.0 STUDY DESIGN AND INVESTIGATIONAL PLAN

3.1 Overview of Study Design

This is a multicenter post marketing surveillance study to monitor the safety of MenACWY-CRM administered according to the prescribing information to 3,300 healthy subjects from 11 to 55 years of age in Korea.

Subjects will be enrolled at the time of their visit to a participating clinic or hospital for vaccination with MenACWY-CRM according to the routine clinical care.

At Visit 1 (Day 1), after obtaining consent from the subjects or subjects' parents/legal representative, the vaccination will be administered. Subjects will remain under observation for at least 30 minutes in the clinic after study immunization.

The subjects or subject's parent/legal representative will be then instructed to complete the Diary Card daily, reporting local and systemic reaction and all other AEs occurring

within 7 days following immunizations, and medically attended AEs or SAEs occurring up to Day 29.

Subjects will also be instructed to return the completed diaries to the study site at Day 29 as follows:

- During a visit at the study center or
- Using the provided pre-addressed stamped envelope (PASE).

At the investigator discretion, the subject or subject's parent/legal representative will be reminded of the date of the study termination by a phone call at Day 29. If any clarification is required after Diary Card retrieval the site staff will follow up by phone, and any additional finding will be recorded on the subject's medical record.

In case the Diary Card is not retrieved within 10 days after Day 29, subject or subject's parent/legal representative will be contacted by phone to assess the occurrence of adverse events, determine the subject's clinical status and complete study termination. All information will be recorded by the site staff on the subject's medical record and collected in the appropriate section of the CRF.

All 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 NVD regional physician to determine whether continued follow up of the SAE is needed.

Table 3.1-1: Safety Assessment Table

Medical History: All significant past diagnoses including all allergies, major surgeries requiring inpatient hospitalization, other significant injuries or hospitalizations, any conditions requiring prescription or chronic medication (i.e., >2 weeks in duration), or other significant medical conditions based on the investigator's judgment.	From birth, collected at clinic visit Day 1
Immediate reactions: Subjects will be assessed for immediate hypersensitivity reactions.	For at least 30 minutes after vaccination
Local reactions: Erythema, induration, pain.	Days 1-7 after vaccination
Systemic reactions: Chills, nausea, malaise, myalgia, arthralgia, headache, rash, fever.	Days 1-7 after vaccination
All unsolicited AEs will be collected	Days 1-7 after vaccination
Medically attended Adverse Events: Events that require a physician's visit or an emergency room visit (*events that are managed by*	From Day 1 to study termination (Day 29/early termination)

telephone or means other than a face-to-face evaluation by a clinician do not qualify as medically attended AEs).	
Serious AEs: All SAEs will be collected.	From Day 1 to study termination (Day 29/early termination)
Medications: Any medications used to treat any solicited local and systemic reaction and unsolicited AE be collected.	From Day 1 to Day 7
Medications: Any medications used to treat any medically attended AE or SAE will be collected.	From Day 1 to study termination (Day 29/early termination)

3.2 Discussion of Overall Study Design

This is a multicenter post-marketing surveillance study to monitor the safety of MenACWY-CRM in Korean individuals from 11 to 55 years of age receiving MenACWY-CRM vaccination according to routine clinical practice and prescribing information.

A total of approximately 3,300 subjects are planned for enrolment into this study, within a 6 years period. Assuming a 10% drop-out rate, this should provide approximately 3,000 evaluable subjects, in compliance with KFDA requirements. Clinics and hospitals including pediatricians and family doctors will be involved in the study.

The study is a post-licensure requirement of the KFDA to provide continued safety evaluation after immunization with MenACWY-CRM in the Korean population.

3.3 Study Procedures and Flowchart

Study subjects or subjects' parent/legal representative will be informed by study staff of the possibility for enrollment in the PMS study while attending a visit at the participating clinic or hospital, for the purpose of vaccination with MenACWY-CRM according to the local routine clinical care.

Informed consent must be obtained from the subject, or where applicable, the subject's parent(s) or legally acceptable representative(s) prior to the performance of any study related procedures.

At the visit, for each subject, data will be collected on the respective source document and then recorded on the appropriate section of the CRF.

Visit 1 - Day 1

- Written informed consent from the subject or subject's parents/legal representative, will be obtained.
- It will be checked whether subject conforms to inclusion and exclusion criteria (see section 4.0).
- Medical history will be collected and recorded on the Medical History CRF.
- A physical exam/assessment, including height, weight and body temperature (preferably axillary) will be performed and results recorded before vaccination.
- Demographic data will be collected and recorded.
- The study vaccine will be administered intramuscularly in the deltoid, preferably of the non-dominant arm. If the investigator determines that the subject's health on the day of vaccination temporarily precludes vaccination, according to the indication reported in the vaccine leaflet, the visit may be rescheduled.
- The subject will be observed closely for at least 30 minutes in the clinic after vaccination, with appropriate medical treatment readily available in case of a rare anaphylactic reaction following the administration of vaccines. Any local or systemic reaction observed within 30 minutes post vaccination will be recorded in the Adverse Event CRF.
- All subjects, or, where applicable, the subject's parents/legal representative, will be dispensed a Diary Card with instructions on how to complete it:
    - Days 1-7: record all local (erythema, induration, pain) and systemic (chills, nausea, malaise, myalgia, arthralgia, headache, rash, fever) reactions, all other AEs and SAEs, and all medications used to treat them;
    - Days 8-29: record all medically attended AEs and SAEs and all medications used to treat them.
- The subjects, or, where applicable, the subject's parent/legal representative, will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.
- The subject or subject's parent/legal representative will be informed of the date of the study termination by a phone call at Day 29, if deemed necessary by the investigator.

☎/✉ - Day 29

- If Diary Cards are returned during a routine visit at the study center, the investigator will review local and systemic reactions, AEs and SAEs with the subject or subject's parent/legal representative. Any new and/or clarified findings, additional

to what was already reported in the Diary Card, will be documented in the subject's medical record;

- If Diary Cards are returned using the PASE, the site staff should carefully review and assess the entries on the Diary Card; for all AEs and SAEs throughout the 28 days following vaccination the site staff should follow up by phone with the subject or subject's parent/legal representative; any new and/or clarified findings should be documented in the subject's medical record.
- All local and systemic reactions noted by the subject or subject's parent/legal representative will be reviewed and recorded on subject's medical record and on the appropriate Local and Systemic Reaction CRF.
- All AEs and SAEs will be collected, reviewed and recorded on the Adverse Events CRF.
- All concomitant medications used to treat AEs and SAEs during the trial will be collected and recorded.

All 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 NVD regional physician to determine whether continued follow up of the SAE is required.

Should the Diary Card not be retrieved within 10 days after Day 29, subject or subject's parent/legal representative will be contacted by phone to assess the occurrence of adverse events, determine the subject's clinical status and complete study termination. All information will be recorded by the site staff on the subject's medical record and collected in the appropriate section of the CRF.

At least three phone contact attempts (at three subsequent days) will be made by the study staff to reach the subject or subject's parent/legal representative.

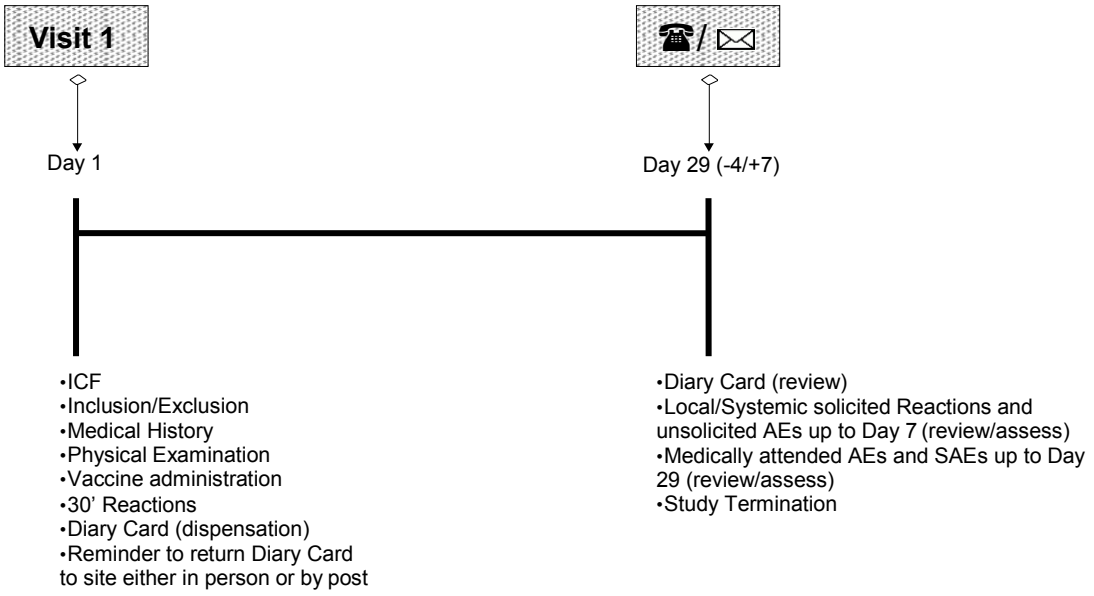
- Study termination will be completed for all subjects and noted on the CRF.

Table 3.3-1: Times and Events Table

Visit Type	Clinic Visit	☎/✉
Study Day	Day 1	Day 29
Study Visit Window	n/a	-4/+7
ICF	X	
Exclusion/Inclusion	X	
Medical history	X	
Physical exam/assessment[a]	X	
Study vaccine administered	X	
Immediate hypersensitivity reactions[b]	X	
Diary Card Dispensed	X	
Diary Card Collected and/or Reviewed[c]		X
Assess/review Local/Systemic Reactions[d]		X
Assess/review AEs and SAEs[e]		X
Concomitant medications[f]	X	X
Study Termination[g]		X

a. Physical examination must be performed by a qualified health professional designated within the Site Responsibility Delegation Log.
b. Data on immediate reactions will be collected by the study personnel for all subjects for 30 minutes post-injection.
c. Diary card review at Day 29 will be performed over the phone or during a routine visit at the study center. Please refer to protocol Section 3.3.
d. Subject's parents/legal representative will record local and systemic solicited reactions on the Diary Card daily for 7 days after each study vaccination.
e. Assess AEs and SAEs according to Safety Assessment Table in the Protocol (Table 3.1-1). All SAEs will be monitored until resolution and/or cause identified. If an SAE remains unresolved at study termination, a clinical assessment will be made by the investigator and the NVD regional physician to determine whether continued follow up of the SAE is needed.
f. Collect concomitant medications according to Safety Assessment Table in the Protocol (Table 3.1-1)
g. Any subject who terminates the study during the Post-Vaccination period is recommended to undergo Day 29 study-related procedures.

Figure 3.3-1: Study Procedure Flowchart - detailed



3.3.1 Data Required by KFDA: Survey Item

The following subject data will be collected and recorded in each subject CRF.

A. Subject Baseline Information

1. Subject Number
2. Demographics: Date of Birth, Sex, Weight, Height
3. Inclusion/Exclusion Criteria
4. Medical History

B. Vaccination Record

1. Pre-Vaccination Body Temperature
2. Date of Vaccination
3. MenACWY-CRM Dose
4. Injection Site

C. Adverse Events

1. Adverse Event
2. Seriousness
3. Date of Onset
4. Date of Resolution
5. Frequency
6. Severity
7. Actions Taken
8. Outcome
9. Relationship to Study Vaccine

D. Concomitant Medications & Vaccine Therapy

1. Name of Drug
2. Route
3. Start and End Date of Therapy
4. Indication for Treatment

E. Study Termination

1. Reason(s) for ending study participation
2. Reason(s) for early termination

3.3.2 Subject Selection Method

In order to obtain information on Regulatory PMS data after market launch, NVD or delegate will create the Regulatory PMS contract with the relevant clinics/hospitals and the physician in charge of the survey shall implement this Regulatory PMS in subjects that receive MenACWY-CRM in the relevant hospital/clinic since the contract date until the number of contracted survey cases, without omission, is reached.

3.3.3 Subject Numbering

In agreement with GCP, each subject will be unambiguously identified by a code, which allows the identification of all the data reported for each subject. In NVD, the code is a 6-digit number resulting from the combination of the site number (first 3 digits) and the subject code (last 3 digits). The site number is assigned by NVD to the investigative site. The digits identifying the subject within the site are assigned sequentially, such as 001, 002, etc. corresponding to the first subject enrolled at each site.

The subject number/identifier is assigned by the investigator after the subject or subject's parent/legal representative has signed the informed consent form and the investigator has confirmed the eligibility criteria. The investigator must keep track of the names of the subjects enrolled and their identifying number in a Subject Identification Code List.

Once assigned to a subject a number cannot be reused.

3.3.4 Method of Assignment to Study Groups

A subject who fulfills all of the inclusion criteria and none of the exclusion criteria is given a subject number/identifier as described above.

3.3.5 Blinding procedures

The study is planned as a single-arm, open-label study for safety monitoring. Study staff and subjects will not be blinded to vaccine administration.

3.3.6 Vaccine Supply, Storage, Tracking and Labeling

The investigational vaccine is MenACWY-CRM conjugate vaccine (Menveo). The vaccine will not be provided by the sponsor. Commercial supplies used in routine clinical practice will be utilized in this study.

The vaccine must be stored by the study centers according to the instructions specified on the labels.

3.3.7 Processing, Labeling and Storage of Serum Samples for Serology

There will be no blood drawn from the subjects during this study.

3.4 Duration of Subject's Expected Participation in the Entire Study

Expected subject trial participation interval: 29 days.

3.5 Stopping/Pausing Rules

There are no predetermined stopping rules other than circumstances for which subjects may be removed from study according to investigator's discretion, as described in section 4.3.

NVD, or the investigator (following consultation with NVD) has the right to discontinue this study at any time. If the study is prematurely terminated, the investigator is to promptly inform the study subjects and should assure appropriate therapy and follow-up for the subjects. All procedures and requirements pertaining to the archiving of the documents should be followed. All other study materials must be returned to the sponsor.

4.0 SELECTION OF STUDY POPULATION

4.1 Inclusion Criteria

Individuals eligible for enrolment in this study are those:

1. male and female subjects from 11 to 55 years of the age at the time of Visit 1 (including all 55 years old subjects, up to one day before their 56th year birthday), who are scheduled to receive vaccination with MenACWY-CRM conjugate vaccine, according to the local prescribing information and routine clinical practice;
2. to whom the nature of the study has been described and the subject or subject's parent/legal representative has provided written informed consent;
3. whom the investigator believes that the subject can and will comply with the requirements of the protocol (e.g., completion of the Diary Card);
4. who are in good health as determined by the outcome of medical history, physical assessment and clinical judgment of the investigator.

4.2 Exclusion Criteria

1. Contraindication, special warnings and/or precautions, as evaluated by the investigators, reported in the MenACWY-CRM conjugate vaccine Korean prescribing information. In particular, should not be included in the study a subject who has ever had:
   - an allergic reaction to the active substances or any of the other ingredients of the study vaccine; an allergic reaction to diphtheria toxoid;

- an illness with high fever; however, a mild fever or upper respiratory infection (for example cold) itself is not a reason to delay vaccination.

Special care should be taken for subjects having haemophilia or any other problem that may stop your blood from clotting properly, such as persons receiving blood thinners (anticoagulants).

4.3 Withdrawal of Subjects from Therapy or Assessment

The subject, or where applicable, the subject's parent/legal representative can withdraw consent for participation in the study at any time without penalty or loss of benefit to which the subject is otherwise entitled. The investigator can withdraw a subject if, in his or her clinical judgment, it is in the best interest of the subject or if the subject cannot comply with the protocol.

If a subject withdraws from the study, the reason for withdrawal should be documented in the subject's medical record and reported in the CRF. If the withdrawal of a subject resulted from an AE, the information should be recorded in the CRF.

Withdrawn subjects will not be replaced.

5.0 TREATMENT OF SUBJECTS

All subjects will be vaccinated with one dose of MenACWY-CRM_{197} (Menveo) on Day 1.

5.1 MenACWY Vaccine

The MenACWY vaccine is supplied as a:

- Vial containing the MenA Lyophilised Conjugate Component as a white to off white powder;
- Vial containing the MenCWY Liquid Conjugate Component as clear solution.

The contents of the two components are to be mixed prior to vaccination providing 1 dose of 0.5 ml.

After reconstitution, one dose of MenACWY will have the following composition per 0,5 mL of injectable solution:

Active substances

- Meningococcal group A oligosaccharide 10 micrograms (*Corynebacterium diphtheriae* CRM_{197} protein 16.7 to 33.3 micrograms)
- Meningococcal group C oligosaccharide 5 micrograms (*Corynebacterium diphtheriae* CRM_{197} protein 7.1 to 12.5 micrograms)

- Meningococcal group W135 oligosaccharide 5 micrograms (*Corynebacterium diphtheriae* CRM_{197} protein 3.3 to 8.3 micrograms)
- Meningococcal group Y oligosaccharide 5 micrograms (*Corynebacterium diphtheriae* CRM_{197} protein 5.6 to 10.0 micrograms)

Stabilizing agent:	Sucrose (EP) - 12.5 mg
Isotonic agent:	Sodium chloride (EP) - 4.5 mg
Buffering agent:	Potassium dihydrogen phosphate (EP) - 5 mM
	Sodium dihydrogen phosphate monohydrate (EP) - 2.5 mM
	Disodium phosphate dihydrate (EP) - 7.5 mM
Diluent:	Water for injections (EP) - 0.5 ml

Following reconstitution the vaccine is a clear, colourless to light yellow solution. One 0.5 mL dose of MenACWY-CRM will be administered by intramuscular (IM) injection in the deltoid area of nondominant arm (preferably).

5.2 Control Vaccines

No control vaccine will be administered during this study.

5.3 Concomitant Vaccines or Treatment

All concomitant medications and concomitant vaccines should be taken by/administered to the subject in accordance with the indication reported in the package leaflet. Concomitant medication and vaccines administered to treat any AE or SAE must be documented on the Concomitant Medications CRF.

5.4 Vaccines Preparation and Administration

The vaccine must be prepared according to the package insert before use.

The principal investigator or designee will be responsible for the administration of the vaccine to subjects enrolled into the study according to the indications reported in package leaflet. The vaccine will be administered only by personnel qualified to perform that function according to the routine clinical practice and under applicable local laws and regulations for the specific study site.

PRECAUTIONS TO BE OBSERVED IN ADMINISTERING STUDY VACCINE:

The vaccination site should be disinfected with a skin disinfectant (e.g., 70% alcohol). Before vaccination, the skin must be dry. **DO NOT inject intravascularly**.

Standard immunization practices should be observed and care should be taken to administer the injection intramuscularly in the deltoid of the non-dominant arm, preferably. As with all injectable vaccines, appropriate medical treatment and supervision should be readily available in case of anaphylactic reactions following administration of the study vaccine. Epinephrine 1:1000 and diphenhydramine, or locally approved medications, should be available in case of any anaphylactic reactions.

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

Vaccination must not be administered to any subject with a clinically significant active infection (as assessed by the investigator) or measured body temperature ≥ 38°C/100.4ºF within 3 days of the intended date of vaccination. If either of these is observed, vaccination should be postponed until the subject's temperature remains below 38.0°C/100.4°F for at least 3 days or the investigator feels that the subject's illness has stabilized, as appropriate.

5.5 Other Concomitant Treatment or Vaccines

Medication taken by the subject prior to the start of the study will not be collected. Other concomitant treatment used during the study period to treat any AE or SAE should be recorded in CRF.

5.6 Vaccination Compliance

The investigator or designee will administer the study vaccine following the indications reported in the package leaflet. The date, dosage, and time of the vaccination must be recorded.

6.0 EFFICACY/IMMUNOGENICITY AND SAFETY ASSESSMENTS

As this is a post-marketing safety monitoring study, efficacy and immunogenicity will not be assessed.

6.1 Appropriateness of Measurements

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

6.1.1 Efficacy/Immunogenicity

Not applicable.

6.1.2 Methods, Criteria and Timing for Assessing and Recording Efficacy/Immunogenicity Parameters

Not applicable.

6.2 Safety Parameters

A brief medical history will be obtained and physical examination performed for each subject entered into the study.

Local and systemic reactions and other adverse events will be collected throughout the study, as detailed in sections 6.2.1 to 6.2.5.

6.2.1 Immediate Hypersensitivity Reactions

The occurrence of immediate hypersensitivity reactions up to 30 minutes after vaccination will be recorded on the Adverse Events CRF.

6.2.2 Local and Systemic Reactions[1]

The occurrence of selected indicators of reactogenicity (listed below), which by definition, can only occur up to 7 days post vaccination, will be recorded on the "Local and Systemic Reactions" appropriate CRF. These will be summarized in the final report under the category "solicited adverse events" to differentiate them from other adverse events which were not solicited.

- **Local Reactions**: erythema, induration and pain.
- **Systemic Reactions**: chills, nausea, malaise, myalgia, arthralgia, headache, rash, fever.

Subjects or subjects' parent/legal representative will be asked to measure body temperature and record all solicited local and systemic reactions and unsolicited AEs for 7 days following vaccination on a Diary Card. The study site will then collect the Diary Card after Day 29 by mail using PASE provided, or at a subsequent clinic or hospital visit. If the Diary Card will not be returned, telephone contacts will be made to solicit assess the occurrence of solicited reactions and adverse event and determine the subjects clinical status.
All other medically attended AEs and associated concomitant medications will be recorded throughout the 29 day follow-up period.

[1] Local and systemic reactogenicity is referred to as "solicited adverse events" to differentiate those events that were solicited on a checklist from other adverse events collected during the trial.

Site staff should consult the MenACWY-CRM Korean prescribing information for additional information concerning contraindications, hypersensitivity, adverse reactions, special warnings and precautions for use.

6.2.3 Adverse Events[2]

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. An AE can, therefore 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.

An unexpected adverse event is one that is not listed in Package Leaflet or an event that is by nature more specific or more severe than a listed event.

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

2. Possibly Related

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

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[2] Adverse Events collected in this study and that are not solicited on a checklist may also be referred to as "unsolicited Adverse Event" in the Clinical Study Report.

3. Probably Related

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

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

6.2.4 Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

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

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 trial (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 trial or was necessary due to a worsening of the pre-existing condition.

6.2.5 Methods and Timing for Assessing and Recording Safety Parameters

All study subjects will be observed for at least 30 minutes after a vaccination for evidence of immediate reactions in general and in particular for symptoms of allergic phenomena

(such as rashes, itching, or other allergic manifestations). Each subject, or where applicable, the subjects' parent/legal representative will be instructed to complete a Diary Card for 28 days following vaccine administration, describing: local reactions, systemic reactions, and all AEs for 7 days after vaccination; medically attended AEs, SAEs and associated concomitant medications throughout 28 days following vaccination. If a local and systemic reaction continues beyond 7 days after vaccination, the subject or subject's parent/legal representative should note this on the Diary Card and note the start and stop dates of the event and any medications used as treatment. When this information is collected by the site, the site staff will record it on the subject's medical record.

The period of observation for adverse events extends from the time the subject receives vaccination until he or she completes the safety follow up period (Day 29) or terminates the study earlier.

Any medical event that occurs after the informed consent form is signed, but prior to receiving study vaccine and is related to a study procedure, will be documented as an adverse event and recorded on the Adverse Events CRF. Any medical event that occurs after the informed consent form is signed, but prior to receiving study vaccine and is not related to a study procedure, will be documented as a pre-existing condition and will be recorded on the Medical History CRF.

All adverse events, regardless of severity, will be monitored by the investigator until resolution or stabilization. All subjects experiencing adverse events - 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. All findings must be reported on an "Adverse Events" CRF and on the "Vaccine Serious Adverse Event" form, if necessary, which is part of the investigator's study file. All findings in subjects experiencing adverse events must be reported also in the subject's medical records.

All SAEs which occur during the course of the trial, whether considered to be associated with the vaccination or not, must be reported **within 24 hours** or at the latest on the following working day by telephone or fax to NVD or designated representatives. Contact details for submitting SAEs to NVD or its designee and instructions for completion of documentation will be provided in a handout located in the Investigator Site File.

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 SAE report, representatives of NVD will contact the investigator if it is necessary to obtain further information for assessment of the event.

NVD will also comply with the applicable regulatory requirements related to the reporting of all SAEs to KFDA.

All SAEs must be reported by the investigator to his/her EC/IRB in accordance with institutional policy/regulation requirements and adequate documentation of this notification must be provided to the sponsor.

If required, a follow up report including all new information obtained on the serious adverse event must be prepared and sent to designated representatives by fax and marked as "Follow-up report."

Post-Study Events

Any AE that occurs outside the protocol-specified observation period or after the end of the study but considered to be caused by the study vaccine must be reported to NVD. These AEs will be processed by the NVD Pharmacovigilance group. Instruction for how to submit these AEs will be provided in a handout in the Investigator File.

6.2.6 Pregnancies

To ensure subjects' safety, each pregnancy in a subject on study vaccine must be reported to NVD within 24 hours of the site learning of its occurrence. If the subject agrees to submit this information, the pregnancy must be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if intended duration of safety follow-up for the study has ended.

Pregnancy data must be recorded on a Pregnancy Report CRF (initial report) and Pregnancy Follow-Up CRF (outcome report) and reported to NVD. Contact details for submitting the case report forms will be described in the Investigator Site File.

Any pregnancy outcome meeting the definition of a SAE (see section 6.2.4) must also be reported on the SAE Report Form.

6.3 Data Monitoring Committee

No Data Monitoring Committee will be convened for this study.

7.0 STATISTICAL PLAN

7.1 Statistical Hypothesis

All analyses will be run descriptively; no statistical (null) hypothesis is associated with the primary safety objective.

7.2 Sample Size and Power Considerations

A total of approximately 3,300 subjects are planned for enrolment into this study. Assuming a 10% drop-out rate, this should provide approximately 3,000 evaluable subjects. This sample size meets the post-licensure requirements of the KFDA to provide continued safety monitoring in the Korean population.

7.3 Population for Analysis

Definition of populations to be analyzed:

(a) All Enrolled Set

All subjects who have signed an informed consent form, undergone screening procedure(s) and received a subject number.

(b) Exposed Set

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

(c) Safety Set

All subjects in the Exposed set who provide post vaccination safety data.

7.4 Analysis of Demographic and Baseline Characteristics

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

7.5 Analysis of Efficacy/Immunogenicity Endpoints

7.5.1 Description of Response Variables

Not applicable.

7.5.2 Statistical Methods for Efficacy/Immunogenicity Variables

Not applicable.

7.6 Analysis of Safety (Endpoints) and Reactogenicity

Analysis of safety criteria

All subjects who receive the immunization and provide some safety data will be considered evaluable for the safety analyses. The safety of the study vaccine will be assessed in terms of number of subjects exposed to study vaccine with reported local and systemic reactions, as well as the number of all subjects with reported AEs and/or SAEs for the specified time period. All SAEs and AEs will be judged by the Investigator as either probably related, possibly related, or not related to vaccine and will be tabulated. All SAEs and AEs resulting in withdrawal from the study will be summarized.

The safety assessment of the study vaccine will be also performed after subject stratification according to age groups. In particular, the following age groups will be analyzed: 11 to 18 years of age; 19 to 34 years of age; 35 to 55 years of age.

7.6.1 Analysis of Extent of Exposure

The number of subjects actually receiving vaccination will be summarized.

7.6.2 Analysis of Local and Systemic Reactions

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

Post-vaccination reactions reported from Day 1 to Day 7 will be summarized by maximal severity. The severity of local reactions, including injection-site, erythema and induration will be categorized as: none (0), 1 to 25 mm; 26 to 50 mm, 51 to 100 mm, >100 mm.

The severity of pain and systemic reactions (i.e., chills, nausea, malaise, myalgia, arthralgia, headache) occurring up to 7 days after each vaccination will be categorized as None, Mild (present but not interfering with daily activity), Moderate (some interference with daily activity), and Severe (prevents daily activity) except for rash, which will be categorized as None, Urticarial, or Other.

Body temperature will be categorized as <38°C (no fever), ≥38°C (fever) and will summarized by 0.5°C increments from 36.0°C up to ≥40°C. Additionally, no fever vs. fever will be reported.

Each local and systemic reaction will also be categorized as none vs. any.

7.6.3 Analysis of Other Adverse Events

All the unsolicited AE occurring from Day 1 to Day 7, and medically attended AE occurring from Day 1 to Day 29 judged either as related to vaccination or not by the investigator, will be recorded as specified in section 6.2.5. The original verbatim terms used by investigators to identify adverse events in the CRFs will be mapped to preferred terms using the most recent MedDRA dictionary. The AEs 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. When an AE occurs more than once for a subject, the maximal severity and strongest relationship to the vaccine group will be counted. Additionally, three separate summaries will be produced: (i) serious adverse events, (ii) medically attended adverse events that are possibly or probably related to vaccine, and (iii) adverse events that are possibly or probably related to vaccine. Data listings of all adverse events will be provided by subject. In addition, a listing of subjects withdrawn from the study because of an adverse event will be presented.

7.7 Planned Interim Analysis

NVD will provide biannual (every 6 months) study status reports during the first two years, and annual reports from the third to the sixth year, in compliance with KFDA requirements.

8.0 STUDY MONITORING, AUDITING AND DOCUMENTATION

Study monitoring and auditing will be performed in accordance with the sponsor's standard operating procedures and applicable regulatory requirements (e.g., KFDA, ICH and GCP guidelines).

Investigators and/or their study staff will be trained on the study protocol and all applicable study procedures prior to subject enrollment. CRFs supplied by NVD must be completed for each enrolled subject. The data entries as well as study related documents will be checked by NVD and/or trained delegates of NVD.

8.1 Study Monitoring

Study progress will be monitored by NVD or its representative (e.g. a CRO) as frequently as necessary to ensure the rights and well-being of study subjects are protected, to verify adequate, accurate and complete data collection, protocol compliance and to determine that the study is being conducted in conformance with applicable regulatory requirements. Arrangements for monitoring visits will be made in advance in accordance with the monitoring plan, except in case of emergency.

8.2 Source Data Verification

Data recorded on the CRF will be verified by checking the CRF entries against source documents (i.e., all original records, laboratory reports, medical records, subjects diaries) in order to ensure data completeness and accuracy as required by study protocol. The investigator and/or site staff must make CRFs and source documents of subjects enrolled in this study available for inspection by NVD or its representative at the time of each monitoring visit.

At a minimum, source documentation must be available to substantiate subject identification, eligibility and participation, proper informed consent procedures, dates of visits, adherence to protocol procedures, adequate reporting and follow-up of adverse events, administration of concomitant medication, study vaccine administration information, and date of completion and reason. Specific items required as source documents will be reviewed with the investigator before the study.

The source documents must also be available for inspection, verification and copying, as required by regulations, by officials of the regulatory health authorities (e.g. KFDA) 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.

The subject or the subject's parents or legally acceptable representative(s) must also allow access to the subject's medical records. Each subject, or the subject's parent(s) or legally acceptable representative(s), should be informed of this prior to the start of the study.

9.0 DATA MANAGEMENT

Three-part "no carbon required" (NCR) paper CRFs will be provided for each subject by the sponsor. All appropriate subject data collected during the study will be recorded on these forms. One copy must be retained by the investigator, and all other copies (including the original copy) will be returned as directed by the sponsor. Instructions on how to complete these forms will be provided to the investigator**.**

All study data must be entered by the investigator or delegate who will sign and date the CRFs. If the investigator delegates and authorizes other persons in his/her staff to make entries on the CRF, the names, positions, signatures and initials must be documented in writing (e.g., site delegation log).

CRFs must be completed during/after each study visit. Arrangements will be made by the study monitor to collect the CRFs upon completion. No CRFs are to be mailed to the sponsor without specific authorization.

Data from the CRFs are entered into the study database by a data management CRO staff member following the Data Management Plan that has been reviewed and approved by NVD. Contact details for the data management CRO are provided in the Data Management Plan.

9.1 Data Handling Procedures

Coding of adverse events, Medical History, and Concomitant Medication will be performed using standard dictionaries as described in the Data Management Plan.

9.2 Documentation of Study Findings

If corrections are made to entries in the CRF by the investigator or designates, the words or figures must be crossed through, leaving the initial entry legible. The correction must then be dated and initialed. Incorrect entries must not be covered with correcting fluid, obliterated, or made illegible in any way. If further corrections are made to a previously reviewed and signed CRF page, the investigator must confirm the correction and endorse the changes by signing and dating the study termination CRF again.

As part of the conduct of the trial, NVD or its representative (e.g. CRO) may have questions about the data after the CRFs are collected from the site. These questions will be documented using Data Clarification Forms (DCFs). The Investigator will provide follow-up clarification and/or resolution of data issues raised by the monitor or the data manager.

An explanation must be provided and documented by the investigator for all missing data.

9.3 Data Protection

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

10.0 RECORD RETENTION

Investigators must retain all study records required by NVD and by the applicable KFDA regulations in a secure and safe facility. The investigator must consult a NVD 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 for PMS in Korea must be retained for 3 years from completion of drug re-examination. Retention time can be prolonged upon KFDA or sponsor request. "Essential documents" are defined as documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents should be retained for a longer period however, if required by the applicable regulatory requirements or by an agreement with the sponsor, but not less that 15 years. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained (ICH E6, 5.5.12).

11.0 USE OF INFORMATION AND PUBLICATION

NVD assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov.

NVD also assures that key results of this study will be posted in a publicly accessible database within one year from the last subject's last study visit (LSLV).

12.0 ETHICS

12.1 Regulatory and Ethical Compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, under KFDA regulations and with the ethical principles laid down in the Declaration of Helsinki.

12.2 Informed Consent Procedures

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), EC/IRB-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the subject. In cases where consent is given by the subject's representative, the subject should be informed about the study to the extent possible given his/her understanding.

Informed consent 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 should be documented in the subject source documents.

NVD will provide to investigators a separate document with a proposed informed consent form that complies with the ICH GCP guideline and regional 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 NVD before submission to the EC/IRB, and a copy of the approved version must be provided to the NVD monitor or its representative (e.g. contract research organization) after EC/IRB approval.

12.3 Responsibilities of the Investigator and IRB/EC

The protocol and the proposed informed consent form will be reviewed and approved by EC/IRB before study start. A signed and dated statement that the protocol and informed consent have been approved by the relevant EC/IRB must be given to NVD before study initiation. A copy of the informed consent must be maintained in the site′s study file.

Prior to study start, 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 NVD monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of NVD, ECs/IRBs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform NVD immediately that this request has been made.

12.4 Protocol Adherence

Investigators will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact NVD or its agents, if any, monitoring the trial 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 NVD and approved by the EC/IRB it cannot be implemented. All significant protocol deviations will be recorded and reported in the clinical study report.

12.5 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 study, potential benefit of the 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 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 NVD, Health Authorities, KFDA where required, and the relevant EC/IRB. In cases when the amendment is required in order to protect the subject safety, the amendment can be implemented prior to relevant EC/IRB 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, NVD should be notified of this action and the relevant EC/IRB at the study site should be informed within 10 working in accordance with local regulations.

13.0 REFERENCE LIST

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.

Cho HK et al. The causative organisms of bacterial meningitis in Korean children in 1996-2005. J Korean Med Sci 2010; 25: 895-899.

Deasy A and Read RC. Challenges for development of meningococcal vaccines in infants and children. Expert Rev. Vaccines 2011; 10: 335–343.

Hill DJ, Griffiths NJ, Borodina E and Virji M. Cellular and molecular biology of *Neisseria meningitidis* colonization and invasive disease. Clinical Science 2010; 118: 547–564.

Korea Centers for Disease Control and Prevention. Communicable diseases monthly report (CDMR). 2007. Online at http://dis.mohw.go.kr/cdmr/cdmr.asp.

Lee JH et al. Etiology of invasive bacterial infections in immunocompetent children in Korea (1996-2005): a retrospective multicenter study. J Korean Med Sci 2011; 26: 174-183.

Moon SY et al. Changing etiology of community-acquired bacterial meningitis in adults: a nationwide multicenter study in Korea. Eur J Clin Microbiol Infect Dis 2010; 29: 793–800.

Obaro S and Madhi S. Bacterial pneumonia vaccines and childhood pneumonia; are we winning, refining, or redefining? Lancet Infect Dis 2006; 6:150-161.

Rouphael NG and Stephens DS. *Neisseria meningitidis*: Biology, Microbiology, and Epidemiology. Methods Mol Biol. 2012;799:1-20.

Song-Mee Bae and Yeon-Ho Kang. Serological and Genetic Characterization of Meningococcal Isolates in Korea. Jpn J Infect Dis. 2008;61:434-437.

Trotter C et al. Effectiveness of meningococcal serogroup C conjugate vaccine 4 years after introduction. Lancet 2004; 364: 365-367.

CLINICAL STUDY PROTOCOL V59_62

Amendment Number 1

A Multicenter Post Marketing Surveillance Study to Monitor the Safety of Novartis Meningococcal ACWY Conjugate Vaccine (MenACWY-CRM) Administered According to the Prescribing Information to Healthy Subjects from 11 to 55 Years of Age in the Republic of South Korea

The present amendment reflects changes to the protocol since the version 1 of the protocol.

DESCRIPTION OF CHANGE(S) AND RATIONALE:

V59_62 is a post-marketing surveillance (PMS) study to monitor the safety of MenACWY-CRM in Korean individuals from 11 to 55 years of age receiving MenACWY-CRM vaccination according to routine clinical practice and prescribing information. The study is a post-licensure requirement of the Ministry of Food and Drug Safety (MFDS) to provide continued safety evaluation in the Korean population. MFDS recently approved (21 March 2013) Menveo indication in subjects 2-10 years of age. The protocol is amended to include these subjects in the PMS study. Solicited local and systemic adverse events are also revised accordingly, to include the definitions relevant to subjects 2 to 5 years of age. Of note, the solicited systemic adverse events reported within V59_62 protocol version 1 were modified as compared to the NVD mandatory standards to ensure consistency with the V59_39 Menveo registration study. NVD standard solicited local and systemic adverse events for subjects < 6 years of age are in included in V59_62 protocol version 2.

V59_62 is conducted in accordance with the principles outlined by MFDS. PMS guidelines require only study protocol and CRF to be submitted for study approval. However, in compliance with NVD SOPs, ICF has also been submitted. Following MFDS approval, some of the IRBs required to provide also an Assent Form to be signed by minors (the age-range for collecting the Assent Form signature is specific for each IRB). The protocol is therefore amended to specify that the Assent Form will be provided to the sites where IRBs specifically requires it.

V59_62 includes individuals receiving MenACWY-CRM vaccination according to routine clinical practice and prescribing information. Exclusion criteria within the protocol descriptively refer to the contraindication contained in the vaccine package leaflet. Exclusion criteria are collected in the database criteria per code, each code associated with a default description. To facilitate the collection of these data in the CDR, a single exclusion criteria referring to the package leaflet is included in the revised protocol.

Korea Food and Drug Administration (KFDA) has changed its official name to Ministry of Food and Drug Safety (MFDS), the protocol is revised accordingly.

CHANGE	LOCATIONS OF CHANGE	RATIONALE FOR CHANGE
Change in target population from 11-55 years of age to 2-55 years of age.	Study title, synopsis, list of abbreviation and definition of terms, section 1, section 2, section 3, section 4, section 7.	Approval for 2-10 years of age subjects granted by MFDS.
Allow Assent Form to be provided to minors when requested by IRBs.	Synopsis, section 3, section 4, section 12.	Assent Form request by some IRBs.
Change in the solicited local and systemic events description.	Synopsis, section 3, section 6, section 7.	Solicited local and systemic events to be described according to NVD standards including the distinction for $\geq$6 years and <6 years of age.
Exclusion criteria numbered.	Section 4.	To facilitate data collection into the CDR.
Change Korea Food and Drug Administration (KFDA) to Ministry of Food and Drug Safety (MFDS)	Synopsis, section 1, section 3, section 4, section 6, section 7, section 8, section 10, section 12.	Change of Regulatory Agency official name

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CLINICAL STUDY PROTOCOL AMENDMENT

Study Number: V59_62

A Multicenter Post Marketing Surveillance Study to Monitor the Safety of Novartis Meningococcal ACWY Conjugate Vaccine (MenACWY-CRM) Administered According to the Prescribing Information to Healthy Subjects from 2 months to 55 Years of Age in the Republic of South Korea

Amendment Number 2

Revised Protocol version 3.0 issued on 22 OCT 14

The present amendment reflects changes to the Revised Protocol version 2.0 issued on 22 MAY 13

The purpose of this amendment is to add infants (2 to 24 months) according to MFDS requirements and add provide clarifications to the protocol.

DESCRIPTION OF CHANGE(S) AND RATIONALE:

CHANGES 1 (Synopsis)

Previously reads:

NA

Now reads:

Infant from 2 to 23 months of age may enroll if scheduled to receive MenACWY-CRM prophylaxis as part of vaccination series per routine standard of care. The infant may enroll at any point, for one injection only, in the vaccination series, including those subjects who may have already initiated the vaccination series.

Rational for changes: Text has been added to clarify the procedure of infant vaccination.

CHANGE 2 (Section 3.3)

Previously reads:

A physical exam/assessment, including height, weight and body temperature (preferably axillary) will be performed and results recorded before vaccination.

Now reads:

A physical exam/assessment, including height, weight and body temperature (preferably axillary **for subjects from 2 to 55 years of age and tympanic for infants**) will be performed and results recorded before vaccination.

Rational for change: Inclusion of infants in standard temperature measurement.

CHANGE 3 (Section 4.2, Exclusion Criteria)

Previously reads:

NA

Now reads:

1. Infants who were already enrolled in this trial for previous vaccination.

Rational for change: To ensure that infants are not enrolled more than once.

CHANGE 4 (Section 6.2.5, Post Study Event)

Previously reads:

Any AE that occurs outside the protocol-specified observation period or after the end of the study but considered to be caused by the study vaccine must be reported to NVD. These AEs will be processed by the NVD Pharmaco-vigilance group.

Now reads:

Any AE that occurs outside the protocol-specified observation period or after the end of the study but considered to be caused by the study vaccine must be reported to the sponsor as spontaneous report as per the local practice.

Rational for change: Spontaneous reporting to be applied to this PMS studies.

CHANGE 5 (Section 6.2.6)

Previously reads:

Pregnancy data must be recorded on a Pregnancy Report CRF (initial report) and Pregnancy Follow-Up CRF (outcome report) and reported to NV.

Now reads:

Pregnancy data must be recorded on a Pregnancy Report CRF (initial report) and Pregnancy Follow-Up CRF (outcome report) and reported to study CRO.

Rational for change: Procedure correction involving the CRO instead of NVD.

CHANGE (Section 7.0, Statistical Plan)

Previously reads:

NA

Now reads:

The statistical plan to analyze and report data according to ICH requirement is described in the following section. A separate document will describe the statistical analysis plan (including population for analysis) according to MFDS.

Rational for change: To clarify that additional SAP will be performed to follow ICH requirements.

Table 1: Other Changes

CHANGE	LOCATION(S) OF CHANGE	RATIONALE FOR CHANGE
Change in the location of the injection including infants. **Menveo is to be administered as a single 0.5 ml intramuscular injection, preferably into the anterolateral aspect of the thigh in infants or into the deltoid muscle (upper arm) in children, adolescents and adults.**	Synopsis Section 3.3 Section 5.1 Section 5.4	Alignment with study population
Change in the study population, adding infants from 2 to 23 months.	Study title Synopsis Section 1; 2 ; 3.1; 3.2; 4.1; 7.2; 7.6	Approval by KFDA

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CLINICAL STUDY PROTOCOL V59_62

A Multicenter Post Marketing Surveillance Study to Monitor the Safety of Novartis Meningococcal ACWY Conjugate Vaccine (MenACWY-CRM) Administered According to the Prescribing Information to Healthy Subjects from 2 months to 55 Years of Age in the Republic of South Korea

Amendment Number 3

Revised Protocol version 4.0 issued on 12 May 2015

The present amendment reflects changes to the Protocol version 3.0

issued on 22 OCT 14

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The purpose of this amendment is to implement changes requested by Korean Health Authorities.

DESCRIPTION OF CHANGE(S) AND RATIONALE:

CHANGE 1

In the synopsis section, page 4, 3rd paragraph, following text was added.

For subjects 2-23 months of age, the parents will also be asked to consent for surveillance after subsequent vaccinations.

CHANGE 2 (*PAGE 23, SECTION 3.3.2)*

Previously read:

In order to obtain information on Regulatory PMS data after-market launch, NVD or delegate will create the Regulatory PMS contract with the relevant clinics/hospitals and the physician in charge of the survey shall implement this Regulatory PMS in subjects that receive MenACWY-CRM in the relevant hospital/clinic since the contract date until the number of contracted survey cases, without omission, is reached.

Now reads:

In order to obtain information on Regulatory PMS data after-market launch, NVD or delegate will create the Regulatory PMS contract with the relevant clinics/hospitals and the physician in charge of the survey shall implement this Regulatory PMS in subjects that receive MenACWY-CRM in the relevant hospital/clinic since the contract date until the number of contracted survey cases, without omission, is reached

Subjects will be enrolled at the time of their visit to participating clinic or hospital for vaccination with MenACWY-CRM according to routine clinical practice:

- Vaccine schedule for children from 2 to 23 months of age
    - In infants initiating vaccination from 2 to 6 months of age, three doses of Menveo, each of 0.5 ml, should be given with an interval of at least 2 months; the fourth dose should be administered during the second year of life with an interval of at least 6 months after the third dose.
    - In unvaccinated children from 7 to 23 months of age, Menveo should be administered as two doses, each as a single dose (0.5 ml), with the second dose administered in the second year of life and at least three months after the first dose.

- Vaccine schedule for children, adolescents and adults 2 to 55 years of age
    - Menveo is to be administered as single dose (0.5 ml).

Subjects 2 to 23 months of age may enroll at any vaccination time point in the vaccination series and will be followed up within the surveillance period for 29 days after vaccination. According to parental consent, these subjects may be followed up for 29 days within the surveillance period after subsequent vaccination(s) at the same study site.

Rationale for Change:

All texts have been changed to align with Korean Heath Authorities.

CHANGE 3 (SECTION 3.3.1)

Previously read:

Table 3.3-1: Times and Events Table

Visit Type	Clinic Visit	
Study Day	Day 1	Day 29
Study Visit Window	n/a	-4/+7
ICF/AF[a]	X	
Exclusion/Inclusion	X	
Medical history	X	
Physical exam/assessment[b]	X	
Study vaccine administered	X	
Immediate hypersensitivity events[c]	X	
Diary Card Dispensed	X	
Diary Card Collected and/or Reviewed[d]		X
Assess/review Local/Systemic Adverse Events[e]		X
Assess/review AEs and SAEs[f]		X
Concomitant medications[g]	X	X
Study Termination[h]		X

Now reads:

Table 3.3-1: Times and Events Table (2 months through 55 years of age)

Visit Type	Clinic Visit	Telephone or Clinic Visit
Study Day	Day 1	Day 29
Study Visit Window	n/a	-4/+7
ICF/AF[a]	X (Only at 1st vaccination)	
Exclusion/Inclusion	X	
Medical history	X	
Physical exam/assessment[b]	X	
Demographics	X (Only at 1st vaccination)	
Study vaccine administered	X	
Immediate hypersensitivity events[c]	X	
Diary Card Dispensed	X	
Diary Card Collected and/or Reviewed[d]		X
Assess/review Local/Systemic Adverse Events[e]		X
Assess/review AEs and SAEs[f]		X
Concomitant medications[g]	X	X
Study Termination[h]		X

Rational for changes: Table was modified to include infant subjects

CHANGE 4 (SECTION 3.3.2)

Previously read:

Adverse events (Not related)

Previously reads:

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

Now reads:

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.

Adverse Events (Possibly related)

Previous reads:

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

Now reads:

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.

Adverse Events (Probably related)

Previously reads:

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

Now reads:

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

Rational for changes: All texts have been changed to align with Korean Heath Authorities.

CHANGE 5 *(*section 3.4)

Previously reads:

Expected subject trial participation interval: 29 days

Now reads:

Expected subject trial participation interval: approximately 29 days

The safety will be followed up until the end of surveillance period, and the end date of surveillance will be informed by the sponsor.

Rational for changes: To clarify study participation duration

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CLINICAL STUDY PROTOCOL V59_62

A Multicenter Post Marketing Surveillance Study to Monitor the Safety of GSK Meningococcal ACWY Conjugate Vaccine (MenACWY-CRM) Administered According to the Prescribing Information to Healthy Subjects from 2 months to 55 Years of Age in the Republic of South Korea

Amendment Number 4

Revised Protocol version 5.0 issued on 25 August 2015

The present amendment reflects changes to the Protocol version 4.0

Issued on 12 May 15

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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 document has been revised to change name of Sponsor.

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