NCT Number:NCT03205371

Immunogenicity and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine Administered Concomitantly with Other Pediatric Vaccines in Healthy Toddlers

Phase III, open-label (immunology laboratory technicians will be blinded to group assignment), randomized, parallel-group, active-controlled, multi-center study to describe the immunogenicity and safety of a single dose of MenACYW conjugate vaccine when administered alone and when administered concomitantly with other pediatric vaccines in healthy toddlers in South Korea, Thailand, the Russian Federation, and Mexico

Statistical Analysis Plan (SAP) - Core Body Part

Trial Code:	MET57
Development Phase:	Phase III
Sponsor:	Sanofi Pasteur Inc. Discovery Drive, Swiftwater, PA 18370-0187, USA
Investigational Product:	MenACYW conjugate vaccine
Form / Route:	Liquid solution / Intramuscular
Indication For This Study:	MenACYW conjugate vaccine as a single dose in toddlers aged 12 to 23 months
Version and Date of the SAP core body part:	Version 2.0, 29NOV2018

Table of Contents

List of Tables

List of Abbreviations

AE	adverse event
BL	blood sample
CI	confidence interval
CRF	electronic case report form
D	day
FAS	full analysis set
GM	geometric mean
GMCs	geometric mean concentrations
hSBA	serum bactericidal assay using human complement
IMD	invasive meningococcal disease
IU	international unit
LLOQ	lower limit of quantitation
MD	missing data
PPAS	per-protocol analysis set
PS	polysaccharide
PT	preferred term
RCDC	reverse cumulative distribution curve
rSBA	serum bactericidal assay using baby rabbit complement
SAE	serious adverse event
SafAS	safety analysis set
SAP	statistical analysis plan
SOC	system organ class (primary)
ULOQ	upper limit of quantitation
WHO	World Health Organization

1 Introduction

This trial will evaluate the immunogenicity and safety of a single dose of the quadrivalent Meningococcal Polysaccharide (Serogroups A, C, Y and W) Tetanus Toxoid Conjugate Vaccine (hereafter referred to as MenACYW conjugate vaccine) in toddlers 12 to 23 months of age

The MenACYW conjugate vaccine is designed for the immunization of individuals of all ages (infants 6 weeks of age and older through and including older adults > 65 years of age) against invasive meningococcal disease (IMD). The purpose of the vaccine is to provide broad coverage against circulating meningococcal strains from serogroups A, C, Y, and W. The MenACYW conjugate vaccine is prepared using tetanus toxoid as the carrier protein. Conjugation of polysaccharide (PS) antigens to a protein carrier can induce T-cell-dependent immune responses, which are anticipated to give rise to higher antibody (Ab) titers, longer duration of the immune response, and enhanced immunologic memory that allows for a booster response. Among the key advantages expected of the tetanus carrier is improved immunogenicity in infants and older adults. Pre-clinical studies using a mouse model and investigating different carriers, showed significant levels of PS-specific total immunoglobulin G (IgG) and bactericidal responses in response to the formulations with tetanus toxoid as a carrier. Early Phase I/II trials including those with the final formulation (MET39 and MET44) showed the potential of the candidate vaccine as a very good immunogen in all age groups, including young infants and older adults. The MenACYW conjugate vaccine was found to be immunogenic and well tolerated; it did not raise any safety concerns in the above trials using the final formulation or in the earlier trials.

The purpose of MET57 is to demonstrate that the immunogenicity and safety profiles of a single dose of MenACYW conjugate vaccine when administered alone in toddlers 12 to 23 months old are comparable to when MenACYW conjugate vaccine is given concomitantly with licensed pediatric vaccine(s), and that the immunogenicity and safety of vaccines routinely administered to toddlers are not affected by concomitant administration with the MenACYW conjugate vaccine.

2 Trial Objectives

2.1 Primary Objective

To describe the immunogenicity profile of MenACYW conjugate vaccine administered alone or concomitantly with licensed pediatric vaccine(s) (MMR+V, DTaP-IPV-HB-Hib, or PCV13).

2.2 Secondary Objective

To describe the immunogenicity profile of licensed pediatric vaccine(s) (MMR+V, DTaP-IPV-HB-Hib, or PCV13) when administered alone or concomitantly with MenACYW conjugate vaccine.

2.3 Observational Objectives

Immunogenicity

To describe the Ab responses to the meningococcal serogroups A, C, Y, and W before and 30 days (+14 days) after vaccination with MenACYW conjugated vaccine measured by serum bactericidal assay using baby rabbit complement (rSBA) in all subjects in Group 1 and Group 2 and in a subset of subjects in Group 4, Group 5, Group 7, and Group 8 (100 subjects per group in Groups 1, 4, and 7; 50 subjects per group in Groups 2, 5, and 8) (South Korea, Mexico, and the Russian Federation only).

Safety

- To describe the safety profile of MenACYW conjugate vaccine when administered alone or concomitantly with licensed pediatric vaccine(s) (MMR+V, DTaP-IPV-HB-Hib, or PCV13)
- To describe the safety profile of licensed pediatric vaccine(s) (MMR+V, DTaP-IPV-HB-Hib, or PCV13) when administered alone or concomitantly with MenACYW conjugate vaccine

3 Description of the Overall Trial Design and Plan

3.1 Trial Design

This is a Phase III, open-label (immunology laboratory technicians will be blinded to group assignment), randomized, parallel-group, active-controlled, multi-center study to describe the immunogenicity and safety of a single dose of MenACYW conjugate vaccine when administered alone compared to when administered concomitantly with other pediatric vaccine(s) in healthy toddlers in South Korea and Thailand (measles-mumps-rubella vaccine [MMR] + varicella vaccine [V]), Mexico (diphtheria, tetanus, acellular pertussis, hepatitis B, poliomyelitis and *Haemophilus influenzae* type-b conjugate vaccine [DTaP-IPV-HB-Hib]), and the Russian Federation (pneumococcal conjugate vaccine [PCV13]).

In South Korea and Mexico, healthy, meningococcal vaccine-naïve toddlers aged 12 to 23 months on the day of enrollment will be randomized in a 2:1:1 ratio (by country) to the following groups:

South Korea:

Group 1: MenACYW conjugate vaccine + MMR + V on Day (D) 0
Group 2: MenACYW conjugate vaccine on D0
Group 3: MMR + V on D0

Mexico:

Group 4: MenACYW conjugate vaccine + DTaP-IPV-HB-Hib vaccine on D0
Group 5: MenACYW conjugate vaccine on D0
Group 6: DTaP-IPV-HB-Hib on D0

In the Russian Federation, healthy, meningococcal-vaccine naïve toddlers aged 12 to 14 months or 16 to 23 months on the day of enrollment will be assigned to Group 8 with a balanced population distribution of half of the subjects aged 12 to 14 months and half of the subjects aged 16 to 23 months. Those aged 15 months on the day of enrollment will be randomized in a 2:1 ratio to Groups 7 and 9 in order to comply with the National Immunization Calendar of the Russian Federation:

The Russian Federation:

Group 7: MenACYW conjugate vaccine + PCV13 on D0
Group 8: MenACYW conjugate vaccine on D0
Group 9: PCV13 on D0

In Thailand, healthy, meningococcal-vaccine naïve toddlers aged 12 to 23 months on the day of enrollment will be randomized in a 2:1:1 ratio to the following groups:

Thailand:

Group 10: MenACYW conjugate vaccine + MMR + V on D0
Group 11: MenACYW conjugate vaccine on D0
Group 12: MMR + V on D0

All Subjects:

All subjects will provide blood samples for immunogenicity assessment at baseline (pre-vaccination) and at Visit 2 (30 to 44 days after vaccination[s]). Solicited AE information will be collected for 7 days after vaccination(s); unsolicited AE information will be collected from Visit 1(D0) to Visit 2, and SAE information will be collected throughout the study period from Visit 1 through Visit 2

3.2 Trial Plan

Vaccination

South Korea (planned number of subjects is approximate)

- Subjects in Group 1 received 1 dose of MenACYW conjugate vaccine, 1 dose of MMR vaccine and 1 dose of V vaccine on D0 (n=100)
- Subjects in Group 2 received 1 dose of MenACYW conjugate vaccine on D0 (n=50)
- Subjects in Group 3 received 1 dose of MMR vaccine and 1 dose of V vaccine on D0 (n=50)

Mexico

- Subjects in Group 4 received 1 dose of MenACYW conjugate vaccine and 1 dose of DTaP-IPV-HB-Hib vaccine on D0 (n=200)
- Subjects in Group 5 received 1 dose of MenACYW conjugate vaccine on D0 (n=100)
- Subjects in Group 6 received 1 dose of DTaP-IPV-HB-Hib vaccine on D0 (n=100)

The Russian Federation

- Subjects in Group 7 received 1 dose of MenACYW conjugate vaccine and 1 dose of PCV13 vaccine on D0 (n=200)
- Subjects in Group 8 received 1 dose of MenACYW conjugate vaccine on D0 (n=100)
- Subjects in Group 9 received 1 dose of PCV13 vaccine on D0 (n=100)

Thailand (planned number of subjects is approximate)

- Subjects in Group 10 received 1 dose of MenACYW conjugate vaccine, 1 dose of MMR vaccine and 1 dose of V vaccine on D0 (n=100)
- Subjects in Group 11 received 1 dose of MenACYW conjugate vaccine on D0 (n=50)
- Subjects in Group 12 received 1 dose of MMR vaccine and 1 dose of V vaccine on D0 (n=50)

Note: A total of 400 subjects were planned to be enrolled in South Korea and Thailand (in Groups 1, 2, 3, 10, 11, and 12). Approximately 200 subjects will be enrolled in South Korea and the remaining subjects will be enrolled in Thailand.

Blood sampling

All subjects were to provide a pre-vaccination blood sample at Visit 0 (screening visit in the Russian Federation only) or Visit 1 (in South Korea, Mexico and Thailand) and a post-vaccination sample at Visit 2 (30 to 44 days after the vaccination[s] on D0).

For sites in the Russian Federation only:

Subjects enrolled at sites in the Russian Federation also provided approximately 2 mL of additional blood sample, (depending on local laboratory needs) for CBC and blood chemistry testing Visit 0 (screening visit) and at Visit 2 (30 days [+14 days] after D0) per Health Authority request and in accordance with local regulations (total blood volume collected was approximately 7 mL per blood draw).

Urine Sampling (for Sites in the Russian Federation Only)

Subjects enrolled at sites in the Russian Federation also provided an approximately 8-mL urine sample (depending on local laboratory needs) for urinalysis before vaccination on Visit 0 and at Visit 2 (30 days [+14 days] after D0) per Health Authority request and in accordance with local regulations.

Collection of safety data (All countries)

- All subjects were observed for 30 minutes after vaccination under the supervision of a responsible healthcare professional at each study site and any unsolicited systemic AEs occurring during that time were recorded as immediate unsolicited systemic AEs in the electronic case report form (CRF).
- The subject's parent / guardian recorded information in a diary card about solicited reactions from D0 to D07 after vaccination(s) and unsolicited AEs from D0 to Visit 2. SAEs were reported throughout the duration of the trial.
- In addition, the subject's parent / guardian were asked to notify the site immediately about potential SAEs at any time during the trial.
- Staff contacted subject's parent / guardian by telephone on D08 (+2 days) to identify the occurrence of any SAE not yet reported and to remind them to complete the diary card up to Visit 2 and to bring it back at Visit 2.
- The completed diary card were reviewed with the subject's parent/ guardian at Visit 2

For the Russian Federation only:

Any clinically significant abnormal results of CBC, blood chemistry, urinalysis, or neurological examination) (according to Investigator judgment) were reported as medical history (for Visit 0 results) or as AEs (for Visit 2 results). All laboratory tests were sampled and analyzed locally. Results of lab tests were assessed by the Investigator. The laboratory values for CBC, blood chemistry, and urinalysis and results of neurological examinations were collected in the CRF if they were clinically significant. Laboratory tests were considered clinically significant in the following circumstances:

- symptomatic
- requiring corrective treatment or additional consultation by relevant specialist
- leading to study vaccine discontinuation or postponing vaccination
- meet SAE criteria

Table 3.1: Study procedures - Subjects in South Korea, Mexico, and Thailand

Phase III Trial, 2 Visits, 1 Vaccination Visit (1, 2, or 3 Vaccinations), 1 Telephone Call, 2 Blood Samples, 30 Days Duration Per Subject

Visit/Contact	Visit 1	Telephone Call	Visit 2
Trial timelines (days)	Day 0	Day 8	Day 30
Time windows (days)	--	+2 days	+14 days
Informed consent	X		
Inclusion/exclusion criteria	X		
Collection of demographic data	X		
Medical history	X		
Physical examination*	X		
Review of temporary contraindications for blood sampling†			X
Randomization/allocation of subject number	X		
Blood sampling (BL), 5 mL‡	BL1		BL2
Vaccination§	X		
Immediate surveillance under supervision by a responsible healthcare professional at each study site (30 minutes)	X		
Diary card provided	X		
Telephone call**		X	
Recording of solicited injection site & systemic reactions	D0 to D07		
Recording of unsolicited AEs	D0 to Visit 2		
Reporting of SAEs	To be reported throughout the study period		
Diary card reviewed and collected			X
Collection of reportable concomitant medications	X		X
Termination of the trial			X

*Temperature needs to be measured and recorded in source documents.

†Should a subject receive oral or injectable antibiotic therapy within 3 days prior to the second blood draw, the Investigator will postpone that blood draw until it has been 3 days since the subject last received oral or injectable antibiotic therapy. Postponement must still be within the timeframe for blood draw (30 to 44 days after vaccination at D0). If postponement would result in the sample collection falling outside of this timeframe, the blood sample should be collected without postponement and it should be documented that the sample was taken less than 3 days after stopping antibiotic treatment.

‡Blood sample at Visit 1 will be drawn before administration of vaccine(s)

§Subjects in **Groups 2, 5, and 11** will receive 1 dose of MenACYW conjugate vaccine. Subjects in **Groups 1 and 10** will receive 1 dose each of MenACYW conjugate vaccine, MMR, and V. Subjects in **Groups 3 and 12** will receive 1 dose each of MMR and V. Subjects in **Group 4** will receive 1 dose each of MenACYW conjugate vaccine and DTaP-IPV-HB-Hib vaccine. Subjects in **Group 6** will receive 1 dose of DTaP-IPV-HB-Hib vaccine.

**This call is made 8 to 10 days after the vaccination at Visit 1. If D08 (+2 days) falls on a weekend or holiday, the telephone call may be made on the following business day. During this telephone call, the staff will find out whether the subject experienced any SAE not yet reported, and will remind the subject's parent/guardian to continue using the diary card up to Visit 2, to bring the diary card to the study center at Visit 2, and confirm the date and time of Visit 2

Table 3.2: Study procedures - Subjects in the Russian Federation Only

Phase III Trial, 3 Visits, 1 Vaccination Visit (1 or 2 Vaccinations), 1 Telephone Call, 2 Blood Samples, 2 Urine Samples, 30 Days Duration Per Subject

Visit/Contact	Visit 0	Visit 1*	Telephone Call	Visit 2
Trial timelines (days)	Day -5	Day 0	Day 8	Day 30
Time windows (days)	+ 5 days	--	+2 days	+14 days
Informed consent	X			
Inclusion/exclusion criteria	X	X†		
Collection of demographic data	X			
Medical history	X			
Physical examination‡	X	X†		
Neurological examination by a neurologist	X§			X
Review of temporary contraindications for blood sampling**				X
Allocation of subject number	X			
Blood sampling (BL) (complete blood count, blood chemistry, and immunogenicity) approximately 7 mL	BL1††			BL2
Urine sample, approximately 8 mL	X‡‡			X
Randomization of subject		X		
Vaccination§§		X		
Immediate surveillance under supervision by a responsible healthcare professional at each study site (30 minutes)		X		
Diary card provided		X		
Telephone call***			X	
Recording of solicited injection site & systemic reactions		D0 to D07		
Recording of unsolicited AEs		D0 to Visit 2		
Reporting of SAEs		To be reported throughout the study period		
Diary card reviewed and collected				X
Collection of reportable concomitant medications	X	X†		X
Termination of the trial				X

*Visit 0 and Visit 1 are separate visits that may take place on the same day. However, Visit 1 can be performed up to 5 days after Visit 0.

†Only performed when activities planned for Visit 1 are not conducted on the same day as Visit 0

‡Temperature needs to be measured and recorded in source documents. When Visit 0 and Visit 1 take place on different days, temperature needs to be measured and recorded at both Visits. Temperature must be measured on the day of vaccination, before administration of vaccine(s).

§ The results (discharge summary) of the neurologist's examination, performed for the subject in terms of routine practice, can be used, if the examination was done within 7 days before Visit 0.

**Should a subject receive oral or injectable antibiotic therapy within 3 days prior to the second blood draw, the Investigator will postpone that blood draw until it has been 3 days since the subject last received oral or injectable antibiotic therapy. Postponement must still be within the timeframe for blood draw (30 to 44 days after vaccination at D0). If postponement would result in the sample collection falling outside of this timeframe, the blood sample should be collected without postponement and it should be documented that the sample was taken less than 3 days after stopping antibiotic treatment.

††The results of CBC and biochemistry laboratory tests, performed for the subject in terms of routine practice, can be used, if the tests were done within 7 days before Visit 0. In this case, the blood sample volume collected at Visit 0 will be 5 mL.

‡‡The results of urine laboratory tests, performed for the subject in terms of routine practice, can be used, if the tests were done within 7 days before Visit 0. In this case, no urine sample will be collected at Visit 0.

§§Subjects in **Group 8** will receive 1 dose of MenACYW conjugate vaccine. Subjects in **Group 7** will receive 1 dose each of MenACYW conjugate vaccine and PCV13 vaccine. Subjects in **Group 9** will receive 1 dose of PCV13 vaccine.

***This call is made 8 to 10 days after the vaccination at Visit 1. If D08 (+2 days) falls on a weekend or holiday, the telephone call may be made on the following business day. During this telephone call, the staff will find out whether the subject experienced any SAE not yet reported, and will remind the subject's parent to continue using the diary card up to Visit 2, to bring the diary card to the study center at Visit 2, and confirm the date and time of Visit 2.

4 Endpoints and Assessment Methods

4.1 Primary Endpoints and Assessment Methods

See Section 9.1 of the protocol.

4.2 Secondary Endpoints and Assessment Methods

See Section 9.2 of the protocol.

4.3 Observational Endpoints and Assessment Methods

See Section 9.3 of the protocol.

4.4 Derived Endpoints: Calculation Methods

4.4.1 Safety

4.4.1.1 Solicited Reactions

4.4.1.1.1 Daily Intensity

All daily records for solicited reactions will be derived into daily intensity according to the following classification: None, Grade 1, Grade 2, Grade 3, or Missing.

For the derivation of daily intensities the following sequential steps will be applied:

1) Solicited reactions (except Fever) with an investigator presence recorded as "No" and with all daily records missing then all daily intensities will be derived as None.

2) For a temperature partially missing after decimal point, the data will be analyzed replacing "MD" (missing data) by zero. For example, a "39.MD" daily temperature will be considered as "39.0°C" at the time of analysis.
3) For non-measurable solicited reactions, daily intensities will correspond to daily records reported in the clinical database. For measurable solicited reactions the daily measurements reported in the clinical database will be converted based upon the intensity scales defined in the protocol; this assumes a reaction that is too large to measure (non measurable, "NM") is Grade 3. Note the intensity could be considered "None" (not a reaction) in the analysis despite being considered a reaction by the investigator (e.g., swelling measurement > 0 mm but < 25 mm in adults).

Note: The maximum intensity on the ongoing period is derived from the record of the maximum intensity/measurement after the end of the solicited period following the rule described above.

4.4.1.1.2 Maximum Overall Intensity

Maximum overall intensity is derived from the daily intensities computed as described in Section 4.4.1.1.1 and is calculated as the maximum of the daily intensities over the period considered.

4.4.1.1.3 Presence

Presence is derived from the maximum overall intensity on the period considered:

- None: No presence
- Grade 1, Grade 2, or Grade 3: Presence
- Missing: Missing presence

Subjects with at least one non-missing presence for a specific endpoint will be included in the analysis. Conversely, those without a non-missing presence will not be included in the analysis of the endpoint.

4.4.1.1.4 Time of Onset

Time of onset is derived from the daily intensities computed as described in Section 4.4.1.1.1. It corresponds to the first day with intensity of Grade 1, Grade 2, or Grade 3.

Note: If a reaction is not continuous (i.e., reaction occurs over two separate periods of time intervened by at least one daily intensity Missing or None) then the time of onset is the first day of the first occurrence.

4.4.1.1.5 Number of Days of Occurrence

Number of days of occurrence over the period considered is derived from the daily intensities computed as described in Section 4.4.1.1.1. It corresponds to the number of days with daily intensities of Grade 1, Grade 2, or Grade 3. Number of days of occurrence on the solicited period with a specified intensity may also be derived.

4.4.1.1.6 Overall Number of Days of Occurrence

If a reaction is ongoing at the end of the solicited period, then the overall number of days of occurrence is derived from the daily intensities and the stop date of the reaction after the end of the solicited period. The overall number of days of occurrence is:

- (stop date – last vaccination date) + (number of days of occurrence within the solicited period) – length of the solicited period + 1

If the stop date is missing or incomplete (contains MD), the overall number of days of occurrence will be considered as Missing.

4.4.1.1.7 Ongoing

Ongoing is derived from the last daily intensity of the solicited period computed as described in Section 4.4.1.1.1 and the maximum intensity on the ongoing period. The investigator's ongoing flag is not used because the measurement would determine the ongoing status of the reaction. Note the intensity could be considered None (not a reaction) in the analysis despite being considered a reaction by the investigator (e.g., swelling measurement > 0 mm but < 25 mm in adults).If the last daily intensity of the solicited period is at least Grade 1 and maximum intensity on the ongoing period is also at least Grade 1, then the reaction is considered ongoing. In any other cases the reaction will not be considered as ongoing.

4.4.1.2 Unsolicited Non-serious AEs

4.4.1.2.1 Presence

An observation will be considered an event if it has at least a verbatim term and is not a Grade 0 intensity event. Grade 0 events should be included in the listing "Unsolicited non-serious adverse events not included in the safety analysis."

4.4.1.2.2 Intensity

Intensity for unsolicited non-serious adverse event (AE) will be derived according to the following classification: None, Grade 1, Grade 2, Grade 3, or Missing.

If the unsolicited non-serious AE is measurable and its preferred term is part of the list of solicited reactions, then the measurement is derived based upon and following the same rule than the intensity scales defined in the protocol for that measurable injection site or systemic reaction. Note the intensity could be considered "None" (not a reaction) in the analysis despite being considered a reaction by the investigator (e.g., swelling measurement > 0 mm but < 25 mm in adults).

Intensity for the other unsolicited non-serious AEs will correspond to the value reported in the CRF.

The maximum intensity corresponds to the highest intensity for a unique term.

4.4.1.2.3 Last Vaccination

Last vaccination before an unsolicited non-serious AE is derived from the visit numbers provided in the clinical database and is calculated as follows:

- If an unsolicited non-serious AE has a non-missing visit number, the visit number should be used to determine the last vaccination before the unsolicited non-serious AE

If the visit number is missing, then the start date should be used to determine the last vaccination before the unsolicited non-serious AE

4.4.1.2.4 Time of Onset

Time of onset is derived from the start date of the unsolicited non-serious AE provided in the clinical database and the date of last vaccination:

- start date of the unsolicited non-serious AE – date of previous vaccination

The time of onset should be considered as missing only if one or both of the dates are missing or partially missing.

The unsolicited non-serious AEs will be analyzed "Within 30 days", which corresponds to AEs with a time of onset between 0 and 30 days after vaccination or missing. An AE with missing time of onset will be considered to have occurred just after the vaccination indicated by the visit number, so will be included in these tables.

Note: Unsolicited non-serious AE that occurred before vaccination (negative time of onset) or with a time of onset higher than defined above will not be included in analysis, but will be listed separately.

4.4.1.2.5 Duration

Duration is derived from the start and stop dates of the unsolicited non-serious AE provided in the clinical database:

- stop date of unsolicited non-serious AE - start date of unsolicited non-serious AE + 1.

The duration should be considered as missing only if one or both of the start and stop dates of the unsolicited non-serious AE is missing or partially missing.

4.4.1.3 SAEs

4.4.1.3.1 Last Vaccination

Last vaccination before an SAE is derived from the last visit numbers provided in the clinical database and is calculated as follows:

- If an SAE has a non-missing visit number, the visit number should be used to determine the last vaccination before the SAE
- If the visit number is missing, then the start date should be used to determine the last vaccination before the SAE

4.4.1.3.2 Time of Onset

Time of onset will be computed using the same methodology as for unsolicited non-serious AEs described in Section 4.4.1.2.4.

SAEs will be analyzed throughout the study using the following periods:

- Within 30 days
- During the study (i.e., all SAEs occurred during the study)

An SAE with missing time of onset will be considered to have occurred just after the vaccination indicated by the visit number, so will be included in these tables.

Note: SAEs that occurred before vaccination (negative time of onset) will not be included in analysis, but will be listed separately.

4.4.1.3.3 Duration

Duration will be computed using the same methodology as for unsolicited non-serious AEs described in Section 4.4.1.2.5.

4.4.1.4 Other Safety Endpoints

4.4.1.4.1 Pregnancy

Not applicable for this study.

4.4.1.4.2 Action Taken

This information will be summarized as collected, including missing observations. No derivation or imputation will be done.

4.4.1.4.3 Seriousness

This information will be summarized as collected. No derivation or imputation will be done.

4.4.1.4.4 Outcome

This information will be summarized as collected. No derivation or imputation will be done.

4.4.1.4.5 Causality

This information will be summarized as collected. Missing causality (relationship) will be handled as described in Section 5.3.1.2.

4.4.1.4.6 AEs Leading to Study Discontinuation

A flag is available in the clinical database for all AEs in order to identify AEs leading to discontinuation.

In general, the items that are counted are:

- Disposition table: A subject who has, on the termination form, the reason for early termination "Serious Adverse Event" or "Other adverse event" checked
- Safety overview table: A subject who has either on the termination form, the reason for early termination "Serious Adverse Event" or "Other adverse event" checked or lists an AE on an AE page (solicited, unsolicited, or SAE) that has "Reaction Leading to Termination" or "Event Leading to Termination" or "Serious Adverse Event Leading to Termination" checked that is at least Grade 1 and is within the time period indicated
- System Organ Class/Preferred Term (SOC/PT) table: An event (solicited, unsolicited, or SAE) that has "Reaction Leading to Termination" or "Event Leading to Termination" or "Serious Adverse Event Leading to Termination" checked that is at least Grade 1 and is within the time period indicated

4.4.2 Immunogenicity

4.4.2.1 Computed Values for Analysis

In order to appropriately manage extreme values (< the lower limit of quantitation [LLOQ] and ≥ the upper limit of quantitation [ULOQ]) for analysis purposes, the following computational rule is applied to the values provided in the clinical database for each BL drawn:

- If a value is < LLOQ, then use the computed value LLOQ/2
- If a value is between ≥ LLOQ and < ULOQ, then use the value
- If a value is ≥ ULOQ, then use the computed value ULOQ

4.4.2.2 Fold-rise

The derived endpoint fold-rise is driven by both baseline and post-baseline computed values and is computed as follows:

- Calculate the fold-rise of values as the ratio of post-baseline computed value divided by baseline computed value

Note: If baseline or post-baseline is missing, then fold-rise is missing.

4.4.2.3 Vaccine response

Vaccine response for PT and FHA antigens:

- If the pre-vaccination concentration is ≥ 4 x LLOQ, then the post-vaccination concentration is ≥ 2 x the pre-vaccination concentration
- If the pre-vaccination concentration is < 4 x LLOQ, then the post-vaccination concentration is ≥ 4 x the pre-vaccination concentration

Then the derived vaccine response rates indicator will be "Yes" for that test, otherwise vaccine response rates will be "No".

4.4.2.4 Vaccine Seroresponse of hSBA

The derived seroresponse indicator for hSBA will be "Yes" if

- hSBA titer is < 1:8 at baseline with a post-baseline hSBA titer ≥ 1:16
- or hSBA titer is ≥ 1:8 at baseline with a ≥ 4-fold increase at post-baseline

4.4.2.5 Vaccine Seroresponse of rSBA

The derived seroresponse indicator for rSBA will be "Yes" if

- rSBA titer is < 1:8 at baseline with a post-baseline rSBA titer ≥ 1:32
- or rSBA titer is ≥ 1:8 at baseline with a ≥ 4-fold increase at post-baseline

4.4.2.6 Efficacy

Not applicable

4.4.3 Derived Other Variables

4.4.3.1 Age for Demographics

The age of a subject in the study was the calendar age in months at the time of inclusion.

4.4.3.2 Duration of a Subject in the Trial

The duration of a subject in the study is computed as follows:

Maximum (date of last visit, date of termination) – (date of Visit 1 of that subject) +1.

4.4.3.3 Duration of the Study

The duration of the study is computed as follows:

Maximum of all subjects (date of last visit, date of termination) – Minimum of all subjects (date of Visit 1) + 1.

5 Statistical Methods and Determination of Sample Size

The statistical analyses will be performed under the responsibility of the Sponsor's Biostatistics platform using SAS® Version 9.4 software or later.

The results of the statistical analysis will be available in the final clinical study report. For descriptive purposes, the following statistics will be presented:

Table 5.1: Descriptive statistics produced

Baseline characteristics and follow-up description	**Categorical data**	Number of subjects. Percentage of subjects.
	Continuous data	Mean, standard deviation, quartiles, minimum, and maximum.
Clinical safety results	**Categorical data**	Solicited: Number and percentage (95% CIs) of subjects. Unsolicited: Number and percentage (95% CIs) of subjects, and number of events.
Immunogenicity results	**Categorical data (seroresponse, ≥ 4 fold rise, cutoff)**	Number and percentage (95% CIs) of subjects.
	Continuous data (titer / concentration)	Log_{10}: Mean and standard deviation. Anti-Log_{10} (work on Log10 distribution, and anti-Log_{10} applied): Geometric mean (GM), 95% CI of the GM. Graphical representation by Reverse Cumulative Distribution Curve (RCDC).

The confidence interval (CI) for the single proportion will be calculated using the exact binomial method (Clopper-Pearson method, quoted by Newcombe (1)). For immunogenicity results, assuming that Log_{10} transformation of the titers follows a normal distribution, at first, the mean and the 95% CI will be calculated on Log_{10} (titers) using the usual calculation for normal distribution (using Student's t distribution with n-1 degree of freedom), then antilog transformations will be applied to the results of calculations, in order to provide GMs and their 95% CI.

5.1 Statistical Methods

5.1.1 Hypotheses and Statistical Methods for Primary Objectives

No hypotheses will be tested. Descriptive statistics will be presented by group and by pooled group for subjects included in South Korea and Thailand (Groups 1 & 10 pooled, Groups 2 & 11 pooled, and Groups 3 & 12 pooled).

5.1.1.1 Statistical Methods

Ab titers against meningococcal serogroups A, C, Y, and W measured by hSBA before and 30 days after vaccination with MenACYW conjugate vaccine will be described by:

- GMT and 95% CI
- Titer distribution and reverse cumulative distribution curves (RCDCs)
- Percentage of subjects with titer ≥ 1:4 and ≥ 1:8 and 95% CI

- Percentage of subjects with titer ≥ 4-fold rise from pre-vaccination to post-vaccination, and 95% CI
- Percentage of subjects with hSBA vaccine seroresponse defined as follows:
    - For a subject with a pre-vaccination titer < 1:8, the post-vaccination titer must be ≥ 1:16
    - For a subject with a pre-vaccination titer ≥ 1:8, the post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer

5.1.2 Hypotheses and Statistical Methods for Secondary Objectives

No hypotheses will be tested. Descriptive statistics will be presented.

5.1.2.1 Statistical Methods

The analyses on the concomitant vaccines will include GMT and titer distribution or GMC, and RCDC, as well as % of subjects with:

- Abs to the antigens contained in MMR vaccine measured before and 30 days after vaccination with MMR vaccine:
    - anti-measles Ab concentrations ≥ 255 mIU/mL
    - anti-mumps Ab concentrations ≥ 10 Mumps Ab units/mL
    - anti-rubella Ab concentrations ≥ 10 IU/mL
- Anti-varicella Ab concentrations before and 30 days (+14 days) after vaccination with V vaccine≥ 5 gpELISA Ab units/mL

- Abs to the antigens contained in DTaP-IPV-HB-Hib vaccine measured before and 30 days after vaccination with DTaP-IPV-HB-Hib vaccine:
    - anti-tetanus Ab concentrations ≥ 0.01 and 0.1 IU/mL at D0 and ≥ 0.1 and 1.0 IU/mL at D30
    - anti-pertussis (PT, and FHA) Ab concentrations and pertussis vaccine response[1]

[1] Pertussis vaccine response:
• If the pre-vaccination concentration is < 4 x LLOQ, then the post-vaccination concentration is ≥ 4 x pre-vaccination concentration;
• If the pre-vaccination concentration is ≥ 4 x LLOQ, then the post-vaccination concentration is ≥ 2 x the pre-vaccination concentration.

- Abs to the antigens contained in DTaP-IPV-HB-Hib vaccine measured 30 days after vaccination with DTaP-IPV-HB-Hib vaccine:
    - anti-diphtheria Ab concentrations ≥ 0.1 and 1.0 international Units (IU)/mL
    - anti-PRP Ab concentrations and ≥ 0.15 and 1.0 µg/mL
    - anti-poliovirus types 1, 2, and 3 Ab titers ≥ 1:8
    - anti-hepatitis B surface antigen Ab concentrations ≥ 10 mIU/mL, ≥ 100 mIU/mL
- Anti-pneumococcal Ab concentrations ≥ 0.35 µg/mL and 1.0 µg/mL and 95% CI for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F measured before and 30 days after vaccination with PCV13 vaccine

5.1.3 Statistical Methods for Observational Objectives

No hypotheses will be tested. Descriptive statistics will be presented by group and by pooled group for subjects included in South Korea and Thailand (Groups 1 & 10 pooled, Groups 2 & 11 pooled, and Groups 3 & 12 pooled).

.

5.1.3.1 Statistical Methods

Immunogenicity

The immunogenicity descriptive analyses will include the following:

Ab titers against meningococcal serogroups A, C, Y, and W measured by rSBA (in 50 subjects per group in Groups 2, 5, and 8; and in 100 subjects per group in Groups 1, 4, and 7) before and 30 days after vaccination with MenACYW conjugate vaccine:

- GMT and 95% CI
- Titer distribution and RCDCs
- Percentage of subjects with titer ≥ 1:8 and ≥ 1:128 and 95% CI
- Percentage of subjects with titer ≥4-fold rise from pre-vaccination to post-vaccination, and 95% CI
- Percentage of subjects with rSBA vaccine seroresponse defined as follow:
    - For a subject with a pre-vaccination titer < 1:8, the post-vaccination titer must be ≥ 1:32
    - For a subject with a pre-vaccination titer ≥ 1:8, the post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer

Safety

For this trial, the safety data will be assessed by applying descriptive statistical methods, supplemented by the calculation of CIs to aid interpretation. The exact binomial distribution (Clopper-Pearson method) for proportions will be used in the calculation of the 95% CIs of events. Analysis tables and listings will contain at least the descriptions listed in Table 5.2

Table 5.2: Statistical analyses for safety observational objectives

Safety Events	Time and Group	Description
Immediate unsolicited systemic AE	Within 30 minutes after injection for all subjects in Groups 1 to 12 at D0	Proportion of subjects that have the event, MedDRA terms, intensity, relationship to vaccine, study discontinuation
Solicited injection site reactions	Up to 7 days after D0 for all subjects in Groups 1 to 12	Proportion of subjects that have the event, onset, duration, intensity, action taken, study discontinuation, temperature collection routes
Solicited systemic reactions	Up to 7 days after D0 for all subjects in Groups 1 to 12	
Unsolicited AE	Up to 30 days after D0 for all subjects in Groups 1 to 12	Proportion of subjects that have the event, MedDRA terms, onset, duration, intensity, relationship, action taken, study discontinuation
SAE	From Visit 1 to Visit 2 for all subjects in Groups 1 to 12	Proportion of subjects that have the event, MedDRA terms, onset, duration, relationship, seriousness criteria, outcome, study discontinuation

5.1.4 Complementary Outputs

Additional analyses by gender will be provided in Appendix 15 of the CSR.

Immunogenicity analyses:

- hSBA GMTs and 95% CI at each time point – Per-Protocol Analysis Set
- Percentage of subjects with hSBA titers ≥ 1:4 and ≥ 1:8 and 95% CI – Per-Protocol Analysis Set
- rSBA GMTs and 95% CI at each time point – Per-Protocol Analysis Set
- Percentage of subjects with rSBA titers ≥ 1:8 and ≥ 1:128 and 95% CI – Per-Protocol Analysis Set

Safety analyses:

Safety overview after vaccine injection –Safety Analysis Set

5.2 Analysis Sets

Three analysis sets will be used: the Full Analysis Set (FAS), the Per-Protocol Analysis Set (PPAS), and the Safety Analysis Set (SafAS).

5.2.1 Full Analysis Set

The FAS is defined as the subset of subjects who received at least one dose of the study vaccine(s) and had a valid post-vaccination blood sample result. All subjects will be analyzed according to the treatment group to which they were randomized.

5.2.2 Per-Protocol Analysis Set

The PPAS is a subset of the FAS. The subjects presenting with at least one of the following relevant protocol deviations will be excluded from the PPAS:

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject did not receive vaccine
- Subject received a vaccine other than the one that he / she was randomized to receive
- Preparation and / or administration of vaccine was not done as per-protocol
- Subject did not provide the post-dose serology sample at Visit 2 in the proper time window or a post-dose serology sample was not drawn
- Subject received a protocol-prohibited therapy / medication / vaccine
- Subject's serology sample at Visit 2 did not produce a valid test result
- Subject had other protocol violation that affected the subject's immune response, as determined by the clinical team prior to locking the database

5.2.3 Safety Analysis Set

The SafAS is defined as those subjects who have received at least one dose of the study vaccine(s) and have any safety data available. All subjects will have their safety analyzed according to the vaccine(s) they actually received. If the vaccine(s) received by a subject does not correspond to any study group, the subject will be excluded from the SafAS. The corresponding safety data will be presented in separate listings.

5.2.4 Populations Used in Analyses

All immunogenicity analyses will be performed on the PPAS. Additional immunogenicity analyses will be performed for exploratory purposes on the FAS. In the FAS, subjects will be analyzed by the vaccine group to which they were randomized.

All safety analyses will be performed on the SafAS. Subjects will be analyzed according to the vaccine(s) they actually received.

5.3 Handling of Missing Data and Outliers

5.3.1 Safety

No replacement will be done. In subject listings, partial and missing data will be clearly indicated as missing.

5.3.1.1 Immediate

For unsolicited non-serious systemic AEs, a missing response to the "Immediate" field is assumed to have occurred after the 30-minute surveillance period and will not be imputed.

For SAEs, missing or partially missing elapsed time from last vaccination recorded if within 24 hours will remain missing and not be imputed. Such SAEs will not be considered as immediate.

5.3.1.2 Causality

Missing causality (relationship) for unsolicited non-serious AEs and SAEs will be considered at the time of analysis as related to vaccination.

5.3.1.3 Measurements

Partially missing temperatures will be handled as described in Section 4.4.1.1.1

5.3.1.4 Intensity

For solicited reactions, missing intensities will be handled as described in Section 4.4.1.1.1. For unsolicited non-serious AEs, missing intensities will remain missing and will not be imputed.

5.3.1.5 Start Date and Stop Date

Missing or partially missing start dates for unsolicited AEs will remain missing and not be imputed. If either the start or stop date is missing or partially missing, the time of onset will be considered to be missing. Nevertheless unsolicited AEs with missing time of onset will be included in analyses according to the visit collected.

Missing or partially missing stop dates for AEs (solicited reactions and unsolicited AEs) will remain missing and not be imputed.

5.3.1.6 Action Taken

Missing actions taken will remain missing and not be imputed.

5.3.2 Immunogenicity

Missing data will not be imputed. No test or search for outliers will be performed.
In order to appropriately manage extreme values (undetectable responses < LLOQ and ≥ [ULOQ]), the following computational rule is applied to the values provided in the clinical database for each BL drawn for analysis purposes:

- If a value is < LLOQ, then use the computed value LLOQ/2
- If a value is between ≥ LLOQ and < ULOQ, then use the value
- If a value is ≥ ULOQ, then use the computed value ULOQ

5.4 Interim / Preliminary Analysis

No interim / preliminary analyses are planned.

5.5 Determination of Sample Size and Power Calculation

[redacted]

5.6 Data Review for Statistical Purposes

A review of the data has been anticipated through the data review process led by data management before database lock. This review of the data included a statistical review.

5.7 Changes in the Conduct of the Trial or Planned Analyses

The SAP core V1.0 was updated to version 2.0 to reflect the changes following amendment 3 of the protocol (version 4.0 dated 11Sep2017; inclusion of study groups in Thailand).

Moreover, for MMRV antigens and in order to reflect the assay used for analysis, the respective thresholds to be considered as clinical endpoint were changed as below:

- anti-measles Ab concentrations ≥ 255 mIU/mL
- anti-mumps Ab concentrations ≥ 10 Mumps Ab units/mL
- anti-rubella Ab concentrations ≥ 10 IU/mL
- anti-rubella Ab concentrations ≥ 5 gpELISA Ab units/mL

Definition of vaccine response for PT and FHA antigens was modified as follow:

- If the pre-vaccination concentration is ≥ 4 x LLOQ, then the post-vaccination concentration is ≥ 2 x the pre-vaccination concentration

- If the pre-vaccination concentration is < 4 x LLOQ, then the post-vaccination concentration is ≥ 4 x the pre-vaccination concentration

6 References List

1 Newcombe R.G., Two-sided confidence intervals for the single proportion: comparison of seven methods, Statistics in Medicine, (1998) 17, 857-72.