16.1.9 Documentation of Statistical Methods

Statistical analysis plan, Version 1.0, Dated 29 August 2018

Statistical analysis plan, Version 2.0, Dated 29 April 2019

PAREXEL International

Serum Institute of India Private Limited (SIIPL); PATH

ACYWX-02 / CVIA058

A Phase 2, Observer-blind, Randomized, Controlled Study to Evaluate the Safety and Immunogenicity of Two Formulations of Investigational Meningococcal Groups ACYWX Conjugate Vaccine, Administered to Healthy Malian Children 12-16 Months of Age

Statistical Analysis Plan

PAREXEL Project Number: 233787

Serum Institute of India Private Limited (SIIPL); PATH
ACYWX-02 /CVIA058 Statistical Analysis Plan

Title: 233787 Interim Analysis Plan 20180627 v1.0 Sign-Off			
Sponsor Project Number:	ACYWX-02/CVIA058	**PAREXEL Project Number:**	233787
Sponsor Name:	Serum Institute of India Private Limited (SIIPL); PATH		

SPONSOR signatures

Signature below indicates that you have reviewed the document for clarity, completeness and consistency and approve it.

Signature 1:

Signature: _____ Date: 10/08/2018

Print Name: Dr. Amol Chaudhari Title: Sr. Manager, Clinical Research, SIIPL

Signature 2:

Signature: _____ Date: _____

Print Name: Yuxiao Tang Title: Biostatistician, Center for Vaccine Innovation and Access, PATH

Serum Institute of India Private Limited (SIIPL); PATH

ACYWX-02 /CVIA058 ACYWX-02 / CVIA058

A Phase 2, Observer-blind, Randomized, Controlled Study to Evaluate the Safety and Immunogenicity of Two Formulations of Investigational Meningococcal Groups ACYWX Conjugate Vaccine, Administered to Healthy Malian Children 12-16 Months of Age

Statistical Analysis Plan

Title: 233787 Interim Analysis Plan 20180627 v1.0 Sign-Off			
Sponsor Project Number:	ACYWX-02/CVIA058	**PAREXEL Project Number:**	233787
Sponsor Name:	Serum Institute of India Private Limited (SIIPL); PATH		

SPONSOR signatures

Signature below indicates that you have reviewed the document for clarity, completeness and consistency and approve it.

Signature 1:

Signature: _____ Date: _____

Print Name: Dr. Amol Chaudhari Title: Sr. Manager, Clinical Research, SIIPL

Signature 2:

Signature: Yuxiao Tang Date: Aug. 7, 2018

Print Name: Yuxiao Tang Title: Biostatistician, Center for Vaccine Innovation and Access, PATH

PAREXEL SIGNATURE PAGE

Signatures below confirm that the review process has been completed in accordance with SOP-GDO-WW-019.

This document has been approved and signed electronically on the final page by the following:

	Signatory
Author	Tianzhe Liu Project Role: Biostatistics Lead
	Signatory
Reviewer	Rukmini Kethireddypally Project Role: Biostatistician
	Kukutla Ramakrishna Project Role: Statistical Programming Lead
	Maiti Kausik Project Role: GMS Reviewer

TABLE OF CONTENTS

RECORD OF MODIFICATIONS

Version Number	Effective Date	Author	Modification Details
0.1	26Apr2018	Kadiroo Jayaraman	New document
0.2	22May2018	Kadiroo Jayaraman	Corrections based on the comments by Rukmini
0.3	5Jun2018	Kadiroo Jayaraman	Corrections based on the comments by Rukmini
0.4	27Jun2018	Kadiroo Jayaraman	Corrections based on the comments from SIIPL/PATH
0.5	07Jul2018	Tianzhe Liu	Correction based on the comments from SIIPL/PATH
1.0	30Jul2018	Tianzhe Liu	Final version 1.0

LIST OF ABBREVIATIONS

AE	Adverse event
ANOVA	Analysis of variance
CI	Confidence interval
CRF	Case report form
CRO	Contract research organization
DSMB	Data Safety Monitoring Board
EPI	Expanded Program on Immunization
FDA	Food and Drug Administration (US)
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
GMTs	Geometric mean titers
GMRs	Geometric mean ratios
IAP	Interim Analysis Plan
ICF	Informed consent form
IP	Investigational Product
IRB	Institutional review board
hSBA	Human complement serum bactericidal activity
MedDRA	Medical Dictionary for Regulatory Activities
NmCV-5	*Neisseria meningitidis* Groups ACYWX Conjugate Vaccine
PHE	Public Health England
PI	Principal Investigator
PT	Preferred term
RCDF	Reverse Cumulative Distribution Function
rSBA	Rabbit complement serum bactericidal activity
SAE	Serious adverse event
SBA	Serum bactericidal activity
SD	Standard deviation
SIIPL	Serum Institute of India Private Limited
SOC	System organ class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TT	Tetanus toxoid
WHO	World Health Organization

1 INTRODUCTION

This study Statistical Analysis Plan (SAP) is applicable to both planned Interim Analysis (IA) and for the preparation of final study report after clinical database lock and unblinding.

As per study protocol, an IA including safety, reactogenicity and immunogenicity results (rSBA) at one month after the first vaccination (Day 28 Visit) will be performed; however, individual listings will not be generated at this point and any access to subject-level information about study groups will be masked. The statistical results that are relevant at Day 28 Visit will constitute IA results.

This study is designed to evaluate safety and immunogenicity of the non-adjuvanted and adjuvanted formulations of the investigational NmCV-5 vaccine in healthy children 12-16 months of age, in comparison with the licensed quadrivalent meningococcal conjugate vaccine (MenACWY-D; Menactra®). Menactra has been selected as an active control given the large safety database accumulated since the vaccine was introduced in the US in 2005, prequalified by WHO and progressively introduced in other countries. Both vaccines will be administered according to a 0, 3 month schedule to meningococcal vaccine-naïve healthy subjects.

This Statistical Analysis Plan (SAP) is based upon the following study documents:

- Study Protocol, Version 2.0 (August 11, 2017)
- Electronic Case Report Form (eCRF), Version 4.0 (November 27, 2017)

This document is in compliance with the requirements of the International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use guideline for Good Clinical Practice ICH E6 –GCP and ICH E9-Statistical Principles of Clinical Trials.

2 STUDY OBJECTIVES

Primary Objective:

1. To assess the reactogenicity of non-adjuvanted and adjuvanted formulations of NmCV-5 vaccine in comparison with the licensed MenACWY-D vaccine, as measured by the percentage of subjects with at least one severe solicited AE reported within 7 days after any vaccination.

Secondary Immunogenicity Objectives:

1. To assess immunogenicity of non-adjuvanted formulation of NmCV-5 vaccine in comparison with MenACWY-D vaccine, as measured by rSBA against serogroups A, C, W, Y and X at 1 month after the second vaccination.

2. To assess immunogenicity of adjuvanted formulation of NmCV-5 vaccine in comparison with non-adjuvanted formulation of NmCV-5 vaccine, as measured by rSBA against serogroups A, C, W, Y and X, at 1 month after the second vaccination.
3. To assess immune responses elicited by non-adjuvanted and adjuvanted formulations of NmCV-5 vaccine and MenACWY-D vaccine at 1 and 3 months after the first vaccination.

Secondary Safety Objective:

1. To evaluate the safety and reactogenicity of adjuvanted and non-adjuvanted formulations of NmCV-5 vaccine in healthy children, when compared to MenACWY-D.

Exploratory Objective:

1. To assess immunogenicity of adjuvanted and non-adjuvanted formulations of NmCV-5 vaccine and MenACWY-D vaccine, as measured by hSBA against serogroups A, C, W, Y and X at baseline, 1 month after the first vaccination and 1 month after the second vaccination (in a subset of subjects).
2. To further assess immunogenicity of adjuvanted and non-adjuvanted formulations of NmCV-5 vaccine and MenACWY-D vaccine, as measured by rSBA against serogroups A, C, W, Y, and X at baseline, 1, month and 3 months after the first vaccination and 1 month after the second vaccination.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a Phase 2, randomized, controlled, observer-blind, single-center study in healthy Malian children 12 to 16 months of age with three vaccination groups.

Duration of the study: The total study duration is approximately 6 months for each subject.

Data collection: Electronic Case Reporting Form (eCRF) and Home Visit Worksheets.

The study vaccination groups:

1. NmCV-5_non-adjuvanted group: approximately 150 subjects receiving the non-adjuvanted formulation of NmCV-5 vaccine at Visit Day 0 and Visit Day 84.

2. NmCV-5_adjuvanted group: approximately 150 subjects receiving the adjuvanted formulation of NmCV-5 vaccine at Visit Day 0 and Visit Day 84.

3. ACWY-D group: approximately 75 subjects receiving the licensed MenACWY-D (Menactra®) vaccine at Visit Day 0 and Visit Day 84.

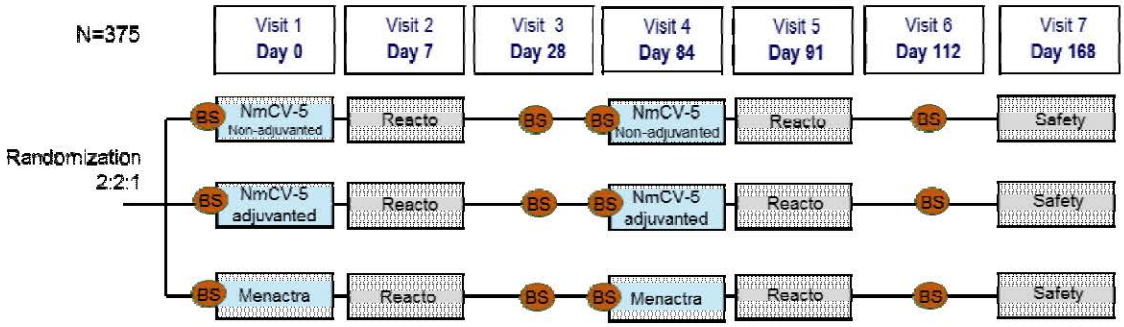
Randomization: At Visit Day 0, prior to the study vaccination, subjects will be randomized into the three study groups according to a 2:2:1 ratio

Vaccination Schedule: 0 and 3 months

Blood sample schedule: Four blood samples (approximately 5 mL each) at Visit 1 (Day 0, first vaccination), Visit 3 (Day 28), Visit 4 (Day 84, second vaccination) and Visit 6 (28 days after second vaccination).

Study visits: Seven visits at Day 0, Day 7, Day 28, Day 84, Day 91 (7 days post Dose 2), Day 112 (28 days post Dose 2) and Day 168 (84 days post Dose 2).

Figure 1. Study design



1. Notes: BS = Blood Sample
2. Written agreement to delay the MenAfriVac dose scheduled at 9 months of age: Prior to written informed consent, subject's parents/guardians may be asked to sign a pre-screening agreement as early as 9 months of age in order to delay the MenAfriVac dose until they can be considered for enrolment in the trial (trial subjects must be at least 12 months of age, have not received any meningococcal vaccines and have not received any vaccinations in the past 28 days).

3.2 Efficacy and Safety Variables

3.2.1 Primary reactogenicity endpoint:

1. Percentage of subjects with at least one severe solicited AE* within 7 days after first vaccination (Days 0-6).

   **Solicited AEs include tenderness, swelling/induration, irritability, drowsiness, decrease of eating, vomiting, and fever*

3.2.2 Secondary immunogenicity endpoints:

1. Percentage of subjects with rSBA titer ≥ 8 against serogroups A, C, W, Y and X at Visits Day 0, Day 28, Day 84 and Day 112.

2. Percentage of subjects with rSBA titer ≥ 128 against serogroups A, C, W, Y and X at Visits Day 0, Day 28, Day 84 and Day 112.
3. Percentage of subjects with fourfold rise in rSBA titers against serogroups A, C, W, Y and X at Visits Day 28 and Day 112.
   - For subjects with a pre-vaccination rSBA titer < 8, a post-vaccination titer of ⩾ 32;
   - For subjects with a pre-vaccination rSBA titer ⩾ 8, an increase in rSBA titer of at least 4 times the pre-vaccination titer.
4. rSBA Geometric Mean Titre (GMT) for serogroups A, C, W, Y and X at Visits Day 0, Day 28, Day 84 and Day 112.

3.2.3 Secondary safety endpoints:

1. Solicited local and systemic AEs reported within 7 days after each vaccination (Days 0-6 and Days 84-90);
2. Unsolicited AEs reported during 28 days after vaccination (Days 0-27 and Days 84-111);
3. AEs leading to premature withdrawal during the entire study period;
4. SAEs reported during the entire study period

3.2.4 Exploratory immunogenicity endpoints:

1. Percentage of subjects with hSBA titer ≥ 8 against serogroups A, C, W, Y and X at Visits Day 0, Day 28 and Day 112 (in a subset of subjects)
2. Percentage of subjects with hSBA seroresponse against serogroups A, C, W, Y and X at Visits Day 28 and Day 112 (in a subset of subjects), defined as:
   - for subjects with baseline hSBA titer < 4, post vaccination hSBA titer ≥ 8;
   - for subjects with baseline hSBA titer ≥ 4, an increase of at least four times the pre-vaccination hSBA
3. hSBA GMTs for serogroups A, C, W, Y and X at Visits Day 0, Day 28 and Day 112 (in a subset of subjects).
4. Percentage of subjects with rSBA titer ≥ 4, ≥ 16, ≥ 32, and ≥ 64 against serogroups A, C, W, Y and X at Visits Day 0, Day 28, Day 84 and Day 112.
5. Percentage of subjects with a fourfold increase in rSBA titers against serogroups A, C, W, Y and X at Visits Day 28 and Day 112 with the following criteria:
   - For subjects with a pre-vaccination rSBA titer < 4, a post-vaccination titer of ⩾ 16;

- For subjects with a pre-vaccination rSBA titer ⩾ 4, a post-vaccination titer of at least 4 times the pre-vaccination titer.

6. Among subjects with a pre-vaccination rSBA titer ≥4, ≥8, ≥16, ≥ 32, ≥ 64, and ≥ 128, percentage of subjects with a post-vaccination titer of at least 4 times the pre-vaccination titer at Visits Day 28 and Day 112.

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard PAREXEL procedures.

The data for the planned IA with a data cut-off date as 7 Apr 2018 will be quality controlled as per applicable PAREXEL standard operating procedures. The data extraction will be set to appropriate date so that all data cleaning activities which includes any corrections to randomization numbers entered at site are taken care of.

4.2 General Considerations for Statistical Analysis and its Presentation

All statistical analyses will be performed using SAS® software Version 9.3 or later.

Medical history and Adverse Events (AE) will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). The frequency count and percentage of subjects will be summarized according to the coded terms of system organ class (SOC) and preferred term. Subject-wise data listing will be provided.

Using the World Health Organization Drug Dictionary (WHO DD), prior and concomitant medications will be tabulated by drug classification, preferred drug name and study group.

Continuous data will also be summarized in terms of the descriptive statistics, number of observations (n), mean, SD, median, minimum, and maximum, unless otherwise stated.

Continuous data that are expected to be skewed will be presented in terms of the maximum, upper quartile, median, lower quartile, minimum and number of observations. The mean, median will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarized in terms of the number of subjects providing data at the relevant time point (N), frequency counts and percentages.

Percentages will be presented to one decimal place. Percentages will be provided even for zero counts. Percentages will be calculated using N as the denominator.

A p-value greater than or equal to 0.001, in general, will be presented to three decimal places, while p-values less than 0.001 will be presented as "<0.001".

Confidence intervals will be presented to one more decimal place than the raw data.

Visit and Observation period Labeling

In tables, listings and figures, visits and observation periods will be labeled using minutes/days up to and including Day 112. Specifically,

Day 0, 30-minutes, Days 0-6, Days 0-27, Days 84-90, Days 84-111, Day 28, Day 84, and Day 112.

All baseline summaries will be presented using label Day 0 (Baseline).

4.3 Study Subjects

4.3.1 Disposition of Subjects

The number of subjects whose parents signed an agreement to defer immunization with MenAfriVac, the number of these subjects subsequently enrolled and the number of subjects who subsequently received MenAfriVac from those not enrolled will be presented. The number of subjects screened, screen failed, eligible, randomized, vaccinated and discontinued will be summarized overall and by vaccination group, as applicable. Subjects who discontinued from the study will also be summarized by reasons for discontinuation as provided in eCRF. A listing of the subject disposition/end of study record for all subjects who discontinued the study prematurely will be produced.

A summary of the number and percentage of subjects who completed, discontinued or had delay in the planned course of study vaccination and the primary reason(s) for discontinuation/delay of study vaccination will be provided. Reasons for study vaccination discontinuation/delay will be presented in the order they are displayed in the eCRF. A listing for study vaccination discontinuation/delay will also be generated by vaccination groups.

Disposition summaries will be based on enrolled population.

4.3.2 Protocol Deviations

Major protocol deviations are defined as those deviations from the protocol that are likely to have an impact on the subject's rights, safety, well-being, and/or on the validity of the data for analysis. This will include all those deviations to be reported in the clinical study report (CSR).

In the event that a subject is allocated the incorrect study treatment as per the study randomization list, it will be considered as a protocol deviation.

The number of subjects with protocol deviations will be summarized by category (Major or Minor) and deviation classification overall and by vaccination group. Protocol deviations will be listed with date and study day of occurrence, deviation category, deviation description and analysis populations from which subject is excluded.

The number of subjects included in each analysis population will be summarized. A listing of subjects included in each analysis population will also be provided. Subject exclusion from analysis sets will be listed with reasons for exclusions.

Above summaries will be based on Exposed population.

4.4 Analysis Populations

Enrolled Population:

All screened subjects who provide informed consent and received a subject ID, regardless of the subject's randomization and treatment status in the trial.

Exposed Population:

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

Immunogenicity Populations:

Immunogenicity analyses will be performed on both the Full Analysis (FA) Population and Per Protocol (PP) Population.

Full Analysis Population

All subjects in the enrolled population who were randomized, received a study vaccination, and provide an evaluable serum sample at least at one time point post-vaccination.

The analysis based on this population will serve as supportive results for all secondary immunogenicity objectives. Subjects in the FA population will be analyzed "as randomized" (i.e., according to the vaccine a subject was designated to receive, which may be different from the vaccine the subject actually received).

Per Protocol Population

All subjects in the FA Population who correctly received two doses of study vaccine per randomization with no major protocol violations that are determined to potentially interfere with the immunogenicity assessment of the study vaccines. This population will serve as the primary analysis population for all immunogenicity objectives.

Due to unpredictability of some irregularities, the criteria for exclusion of subjects from the Per Protocol Population will be determined before the database is locked and will be based on the blinded review of protocol violations.

Safety Population:

All subjects in the enrolled population who received a study vaccination and had any safety data available.

Subjects will be analyzed as "treated" (i.e., according to the actual vaccine received at the first dose). All safety analyses will be performed using this population. The denominators for different safety endpoints may vary according to the number of subjects with available data for the specific endpoint. For example, the solicited adverse event endpoints will be based only on those who have the corresponding CRF data regardless of other safety follow-up data.

Decisions regarding the exclusion of subjects and/or subject data from analyses will be made prior to unblinding during blinded data review meeting and will be documented and approved by the SIIPL/PATH.

4.5 Demographic and Other Baseline Characteristics

4.5.1 Demographics and Baseline Characteristics

Descriptive statistics (number of subjects, mean, standard deviation, median, minimum and maximum) for age, length and weight at enrolment will be calculated by overall and by vaccine group. Distributions of subjects by gender, race and ethnicity will be summarized (using counts and percentages) overall and by vaccine group. Baseline characteristics include vital signs, temperature, heart rate, and respiratory rate. Baseline characteristics will be listed and summarized (number of subjects, mean, standard deviation, median, minimum and maximum).

Demographic summaries will be based on enrolled population who are randomized.

4.5.2 Medical History

Medical conditions will be coded by the medical dictionary for regulatory activities (MedDRA). The final MedDRA version to be used will be decided prior to database lock.

Medical conditions present at screening will be summarized and listed. They will be summarized by SOC and preferred term. These will be based on exposed population.

4.5.3 Prior and Concomitant Therapies

Prior and concomitant therapies will be coded by World Health Organization – Drug Dictionary (WHOB2B3HERBAL Dictionary).

4.5.3.1 Prior Medications and Vaccines

The following are considered prior medications for this study:

- any investigational or non-registered product (drug or vaccine) received prior to enrolment;
- any vaccine administered prior to enrolment;
- any immunosuppressant or other immune-modifying drug including systemic steroids, within 3 months prior to enrolment;
- any blood, blood product and/or plasma derivative or any parenteral immunoglobulin preparation within 3 months prior to enrolment;
- any systemic antibiotic within 3 days prior to enrolment;
- Any antipyretic/analgesic within 24 hours prior to first vaccination.

If above medications were administered to the subject within the specified window prior to the first study vaccination, they will be recorded on the Concomitant Medications page of eCRF.

Prior medications and vaccines will be listed and summarized. They will be summarized by generic preferred name, and Anatomical Therapeutic Chemical (ATC) class. More than one ATC class per medication is possible and the medication will be reported under all applicable classes. A subject with multiple occurrences within a ATC class is counted only once for that ATC class; similarly a subject with multiple occurrences within a generic preferred name, is counted only once.

4.5.3.2 Concomitant Medications, Vaccines, Non-drug Treatment and Procedures

Medications taken at any time during the study period are considered as concomitant medications and will be summarized by vaccination group in the exposed population.

Concomitant medications and vaccines will be listed and summarized similar to Prior medications.

The non-drug treatment and procedures captured in eCRF will be listed and summarized. They will be summarized by System Organ Class (SOC) and preferred term.

Prophylactic Antipyretics / Analgesics

Medications taken for prophylaxis are those administered in the absence of any symptom and intended to prevent the onset of post-vaccination symptoms. Medications taken for treatment are intended to reduce or eliminate the symptoms that are present.

The antipyretics and/or analgesic medications taken within 24 hours prior to the study vaccination recorded in eCRF will be listed and summarized.

The antipyretics / analgesics administered after study vaccination and the reason for their use (prophylaxis versus treatment) will be listed and summarized based on recorded data in source documents and Concomitant Medications eCRF.

4.6 Treatment Compliance

No treatment compliance measures are included in this study.

4.7 Efficacy Evaluation

4.7.1 Analysis and Data Conventions

The primary objective is to evaluate the reactogenicity of adjuvanted and non-adjuvanted formulations of NmCV-5 vaccine in comparison with the licensed comparator (Menactra®). The secondary objectives are to assess safety and the immune response of adjuvanted and non-adjuvanted formulations of NmCV-5 vaccine.

4.7.1.1 Multi-center Studies

The study is conducted in a single center.

4.7.1.2 Adjustments for Covariates

No analysis specified includes adjustment for covariates.

4.7.1.3 Handling of Dropouts or Missing Data

Missing data will not be imputed and will be analyzed as if they were randomly missing.

The number and percentage of subjects with missing data for the primary and secondary endpoints will be summarized by treatment group and overall.

4.7.1.4 Multiple Comparisons/Multiplicity

Due to hypothesis generating nature of this study, all statistical comparisons for reactogenicity, safety, and immunogenicity endpoints will be carried out without an adjustment for multiple comparisons. All statistical tests except for non-inferiority will be two-sided with a type I error rate of 5%. Non-inferiority tests will be one-sided with type

I error of 2.5%. The 95% confidence interval will be presented for estimates as described later.

4.7.1.5 Interim Analyses

An interim analysis including safety, reactogenicity and immunogenicity results (rSBA) at 1 month after the first vaccination will be performed. Individual listings will not be generated at this point and any access to subject-level information about study groups will be masked.

The objective of Interim Analysis (IA) is to compare treatment groups one month post first vaccination with respect to the immunogenicity responses so as to make a choice among the two NmCV-5 formulations for use in future clinical development. Comparisons with regard to safety and reactogenicity also will be performed, as applicable.

For presentation of IA immunogenicity summary results, table layouts will be generated in such a way that study blind is broken only at the treatment (i.e., vaccine) group level, but there shall not be any subject level unblinding. The study disposition, protocol deviation, demographic, and safety data will also be presented by group level; however, unlike the immunogenicity results, the treatment (i.e., vaccine) *per se* will not be identified and the groups will be labelled Vaccine 1, 2, and 3. Moreover, no actual subject numbers will be presented, neither numerators nor denominators, and only percentages will be presented for individual groups. This process will help minimize any potential subject-level unblinding. Individual subject listings will be generated for purposes of statistical quality control and will not be circulated to any blinded members at PAREXEL, sponsor or site.

Where possible, IA results will use table layouts that can be included in final study ICH E3 Clinical Study Report.

Database soft-lock has to be achieved on the data to be used for IA after cleaning. An IA snapshot of the database along with IA results will be stored in password protected area within statistical reporting systems of PAREXEL until final database lock and unblinding is achieved.

The interim analysis results will only be circulated to pre-specified representatives of SIIPL and PATH and will not be circulated to the Investigators or any other site staff.

4.7.1.6 Examination of Subgroups

No subgroup analysis is planned for this study.

4.7.2 Statistical Methods for Primary Objective

Precision estimates of the percentages of subjects with at least one severe solicited AE reported within 7 days after any vaccination will be computed by vaccine group using the two-sided 95% Clopper-Pearson confidence intervals.

The differences between groups (Group NmCV-5_non-adjuvanted - Group MenACWY-D and Group NmCV-5_adjuvanted - Group MenACWY-D) in the percentages of subjects with at least one severe solicited AE reported within 7 days after any vaccination will be provided along with their two-sided 95% CIs obtained by the Miettinen and Nurminen method. The details of the Miettinen and Nurminen method are provided in the Appendix 1.

4.7.3 Statistical Methods for Secondary Objectives

4.7.3.1 Analysis of Secondary Immunogenicity Objectives

For all rSBA titers reported as "<4" will be treated as "2" in immunogenicity analysis.

Per protocol population will be used as primary analysis population for assessing immunogenicity objectives.

Supportive analyses of immunogenicity objectives will be based on full analysis population.

Proportion of subjects with antibody response greater than or equal to the cut-off (e.g. rSBA titer ≥ 8 or 128) at Visits Day 0, Day 28, Day 84 and Day 112 and proportion of subjects with four-fold increase from baseline at Visits Day 28 and 112.

For each *N. meningitidis* serogroup A, C, W, Y, and X the percentages of subjects with rSBA titers ≥ 8 and the corresponding exact two-sided 95% CIs based on Clopper-Pearson method will be calculated for each study group at baseline (Day 0), one and three months after the first vaccination (Day 28 Visit, Day 84 Visit) and one month after the second vaccination (Day 112 Visit).

Similar calculations will be repeated with cutoff of rSBA titers ≥ 128.

For each of N. *meningitidis* serogroup A, C, W, Y, and X the percentages of subjects with four-fold rise (for subjects with a pre-vaccination rSBA titer < 8, a post-vaccination titer of ⩾ 32; for subjects with a pre-vaccination rSBA titer ⩾ 8, an increase in rSBA titer of at least 4 times the pre-vaccination titer) in post vaccination rSBA titers from baseline and the corresponding exact two-sided 95% CIs based on the Clopper-Pearson method will be calculated for each study group at one month after the first vaccination (Day 28 Visit) and one month after the second vaccination (Day 112 Visit).

At Day 112 Visit and for each of N. *meningitidis* serogroup A, C, W, Y, and X, and for each rSBA titer ≥ cut-off (8,128), the difference in percentages between NmCV-5 non-

adjuvanted group and MenACWY-D group and between NmCV-5 non-adjuvanted group and NmCV-5 adjuvanted group will be provided along with the two-sided 95% CIs that will be constructed using the method of Miettinen and Nurminen. Similar comparisons will be provided between NmCV-5 adjuvanted group and MenACWY-D group at Day 112 Visit. Similar analysis will be repeated at Day 28 and Day 84 Visits. At Day 28 and 112 Visits, similar comparisons will be provided for four-fold rise in post vaccination rSBA.

Let P_{NNSG}, P_{NASG} and P_{MNSG} represent the corresponding percentages of subjects with rSBA titers ≥ 8 for a given serogroup for NmCV-5 non-adjuvanted, NmCV-5 adjuvanted and MenACWY-D groups, respectively. We will test the following hypotheses,

H_{01}: $P_{NNSG}-P_{MNSG} \leq -10\%$ versus H_{a1}: $P_{NNSG}-P_{MNSG} > -10\%$
H_{02}: $P_{NNSG}-P_{NASG} \leq -10\%$ versus H_{a2}: $P_{NNSG}-P_{NASG} > -10\%$

We can form similar hypotheses for the case of rSBA titers ≥ 128 and four-fold rises.

At one month post second vaccination (Day 112 Visit), for a given titer cut-off, if the lower limit (LL) of 95% confidence interval (CI) for difference in percentages between NmCV-5 non-adjuvanted group and MenACWY-D group or between between NmCV-5 non-adjuvanted group and NmCV-5 adjuvanted group is above -10% (commonly accepted non-inferiority margin) for each serogroup A, C, W, Y, and X then non-inferiority of NmCV-5 non-adjuvanted group to MenACWY-D group or NmCV-5 non-adjuvanted group to NmCV-5 adjuvanted group will be demonstrated for each corresponding endpoint, respectively. Similar comparisons will be provided between NmCV-5 adjuvanted group and MenACWY-D group. Similar analysis will be repeated at one month post first vaccination (Day 28 Visit).

rSBA GMT for serogroups A, C, W, Y and X at Visits Day 0, Day 28, Day 84 and Day 112.

The rSBA titers at each visit (Day 0, Day 28, Day 84, and Day 112) for each study group will be logarithmically transformed (base 2) to fulfil the normal distribution assumption. For each study group, *N. meningitidis* serogroup (A, C, W, Y, and X) at each visit Day 0, Day 28, Day 84, and Day 112, the GMTs will be calculated with their associated two-sided 95% CIs, by exponentiating the corresponding log-transformed means and their 95% CIs.

For each study group, *N. meningitidis* serogroup (A, C, W, Y, and X) at each post vaccination visit Day 28, Day 84, and Day 112, the logarithmically transformed rSBA change from baseline (Day 0) will be obtained. The Geometric Mean Ratio (GMR: post vaccination/baseline) will be calculated with their associated two-sided 95% CIs, by exponentiating the corresponding log-transformed means and their 95% CIs.

For each of the five vaccine serogroups at Day 112 Visit, the comparison of GMTs and GMRs will be made using one-way analysis of variance (ANOVA) containing term for vaccine group, with the logarithmically transformed rSBA titres as a dependent variable. Similar analysis will be repeated at Day 28 and Day 84 Visits.

The ratio of GMTs between the study vaccination groups and the corresponding 95% CIs will be constructed by exponentiating the mean difference and the confidence limits in log2 (titer) obtained within ANOVA. Similarly, the logarithmically transformed rSBA change from baseline will be analysed using ANOVA to obtain ratio of GMRs and their associated 95% CIs.

In addition, a reverse cumulative distribution plot of each immunogenicity measure will be created. Reverse cumulative distribution function (RCDF) refers to the complement of cumulative distribution function given by the following function.

$$\text{RCDF} = 1 - \text{CDF} = 1 - \int_{-\infty}^{x} f(x)dx$$

RCDF will be generated for all the immunogenicity measures for each serogroup by treatment group. Empirical RCDF will be generated for each titer measure and superimposed in graphs with similar values based on lognormal function. Cutoff points of 8 and 128 indicated in the graphs.

4.7.3.2 Statistical Methods for Exploratory Immunogenicity Objective

Exploratory immunogenicity endpoints w.r.t rSBA titer

(a) Percentage of subjects with rSBA titer ≥ 4, ≥ 16, ≥ 32, and ≥ 64 against serogroups A, C, W, Y and X at Visits Day 0, Day 28, Day 84 and Day 112

(b) Percentage of subjects with a fourfold increase in rSBA titers against serogroups A, C, W, Y and X at Visits Day 28 and Day 112 with the following criteria:

- For subjects with a pre-vaccination rSBA titer < 4, a post-vaccination titer of ⩾ 16;
- For subjects with a pre-vaccination rSBA titer ⩾ 4, a post-vaccination titer of at least 4 times the pre-vaccination titer.

(c) Among subjects with a pre-vaccination rSBA titer ≥4, ≥8, ≥16, ≥ 32, ≥ 64, and ≥ 128, percentage of subjects with a post-vaccination titer of at least 4 times the pre-vaccination titer at Visits Day 28 and Day 112.

For each N. meningitidis serogroup the percentages of subjects with rSBA ≥4, ≥16, ≥ 32, and ≥ 64 and the corresponding exact two-sided 95% CIs based on Clopper-Pearson method will be calculated for each study group at baseline (Day 0), one (Day 28 Visit) and three months (Day 84 Visit) after the first vaccination and one month after the second vaccination (Day 112 Visit).

Percentages of subjects with four-fold rSBA titer rise with criteria described in exploratory immunogenicity endpoints for rSBA and the corresponding exact two-sided 95% CIs based on the Clopper-Pearson method against these serogroups will be calculated for each study group at one month after the first vaccination (Day 28 Visit) and one month after the second vaccination (Day 112 Visit).

Exploratory Immunogenicity endpoints related to hSBA titer:

Whenever the hSBA testing is performed and the results available, the analyses related to corresponding exploratory endpoints will be performed as follows,

(a) Percentage of subjects with hSBA titer ≥ 8 against serogroups A, C, W, Y and X at Visits Day 0, Day 28 and Day 112 (in a subset of subjects)

(b) Percentage of subjects with hSBA seroresponse against serogroups A, C, W, Y and X at Visits Day 28 and Day 112 (in a subset of subjects), defined as:

- for subjects with baseline hSBA titer < 4, post vaccination hSBA titer ≥ 8;
- for subjects with baseline hSBA titer ≥ 4, an increase of at least four times the pre-vaccination hSBA

(c) hSBA GMTs for serogroups A, C, W, Y and X at Visits Day 0, Day 28 and Day 112 (in a subset of subjects).

For each *N. meningitidis* serogroup the percentages of subjects with hSBA titers ≥ 8 and the corresponding exact two-sided 95% CIs based on Clopper-Pearson method will be calculated for each study group at baseline (Day 0), one month after the first vaccination (Day 28) and one month after the second vaccination (Day 112).

Percentages of subjects with hSBA seroresponse and the corresponding exact two-sided 95% CIs based on the Clopper-Pearson method against these serogroups will be calculated for each study group at one month after the first vaccination (Day 28) and one month after the second vaccination (Visit Day 112).

Post vaccination at Day 28 and Day 112 Visits, for each of N. *meningitidis* serogroup A, C, W, Y, and X, and for each of hSBA endpoints (a) & (b), the difference in percentages between each of the NmCV-5 (adjuvanted and non-adjuvanted) groups and MenACWY-D group as well as between the adjuvanted and non-adjuvanted NmCV-5 groups will be provided along with the two-sided 95% CIs that will be constructed using the method of Miettinen and Nurminen.

For each *N. meningitidis* serogroup, the hSBA titers at each visit (Days 0, 28, 112) for each study group will be logarithmically transformed (base2) to fulfil the normal distribution assumption.

The ratio of GMTs between each of the NmCV-5 (adjuvanted and non-adjuvanted) groups and MenACWY-D group as well as between the adjuvanted NmCV-5 vs non-adjuvanted NmCV-5 study groups and the corresponding 95% CIs will be constructed by

exponentiating the mean difference and the confidence limits in log2 (titer) obtained within ANOVA. Similarly the logarithmically transformed hSBA change from baseline will be analysed using ANOVA to obtain ratio of GMRs (post vaccination / baseline) and their associated 95% CIs.

In addition, a reverse cumulative distribution plot of each measure will be created.

4.7.3.3 Secondary Safety Objectives

The design of the study allows a comparison among groups after each vaccination and after any vaccination. All solicited adverse events will be summarized according to defined severity grading scales.

Analysis of Solicited Adverse Events

All solicited adverse events will be summarized according to defined severity grading scales. Frequencies and percentages of subjects experiencing each adverse event will be presented for each symptom severity. Summary tables showing the occurrence of any local or systemic adverse event will also be presented.

The difference between groups (Group NmCV-5_non-adjuvanted - Group MenACWY-D and Group NmCV-5_adjuvanted - Group MenACWY-D) in percentage of subjects with at least one local or systemic adverse event overall and at each time point will be calculated along with their two-sided 95% CIs obtained using the Miettinen and Nurminen method.

Post-vaccination solicited adverse events reported from Day 0 to Day 6 will be summarized by severity and by vaccine group. Separate analysis will be performed for solicited AEs reported 30 minutes after vaccination. All the solicited reactions occurring up to 7 days after each vaccination will be summarized according to severity grading based on the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events provided in Appendix II of the protocol.

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

Use of antipyretics and analgesics will be summarized by frequency, by type of use (prophylactic versus treatment) and percentage of subjects reporting use.

Body temperature will be summarized separately according to the 2 schemes described below.

Temperature schemes.

- by 0.5 °C increments from 36.0°C up to ≥40°C
- <36.0, ≥36.0-<37.0, ≥37.0-<38.0, ≥ 38.0-<39.0, ≥39.0-<40, ≥40°C

Analysis of Unsolicited Adverse Events

All the adverse events occurring during the study, judged either as related, or not related to vaccination by the investigator, will be recorded.

The original verbatim terms used by investigators to identify adverse events in the eCRFs will be mapped to preferred terms using the MedDRA dictionary. The adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class. All reported adverse events, including adverse events judged by the investigator as related to study vaccine, will be summarized according to system organ class and preferred term within system organ class. When an adverse event occurs more than once for a subject, it will be considered as multiple events and each event will be presented distinctly.

The summaries will be presented by period of onset and will include frequency distributions of the different adverse events:

- All unsolicited AEs reported within 28 days after each vaccination;
- AEs leading to premature withdrawal from the study during the entire study period;
- SAEs reported during the entire study period.

The analysis of unsolicited adverse events comprises the following categories:

- Any unsolicited AEs;
- Related unsolicited AEs;
- SAEs;
- Related SAEs;
- Unsolicited AEs leading to withdrawal from the study;
- Unsolicited AEs leading to withdrawal from study vaccination but remaining in the study;
- Unsolicited AEs leading to hospitalization;
- Any AEs leading to death.

Data listings of all adverse events will be provided by subject.

- For IA details of safety endpoints see Section 4.7.1.5

4.8 Safety Evaluation

Safety evaluation forms the secondary objectives in this study and is already discussed in section 4.7.3.3.

4.8.1 Extent of Exposure

The number and percentage of randomized subjects who completed the planned course of study vaccination will be summarized by study day, vaccination group and overall. The number and percentage of subjects who discontinued from the study vaccination will also be summarized by study day, vaccination group and overall.

These summaries will be provided for the exposed population.

4.8.2 Adverse Events

The reporting of adverse events is already discussed in section 4.7.3.3. Some additional information is given in the following.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1 or later. If a subject experiences an adverse event more than once, the event at the most severe occurrence will be considered. However, the number of events occurred will also be included in the summary tables. Subjects will be included only once in the total for a body system where they experienced one or more events.

Adverse event summaries will be ordered in terms of decreasing frequency for System Organ Class (SOC), and Preferred Term (PT) within SOC for all the vaccine groups and then alphabetically for SOC, and PT within SOC.

For each subject and each adverse event, the worst severity recorded will be attributed and used in the by-severity summaries. Similarly, the worst causality (most related to treatment) will be attributed and used in the by-causality summaries. If severity or causality is missing, the worst case will be assumed. Where multiple recordings of the same event are recorded, the number of such events will be tabulated.

4.8.3 Deaths, Serious Adverse Events, and Other Significant Adverse Events

Deaths and SAEs will be summarized by treatment group including severity, relatedness and seriousness criteria.

4.8.4 Clinical Laboratory Evaluation

This study has no safety laboratory measurements.

4.8.5 Vital Signs, Physical Findings and Other Observations Related to Safety

Other than temperature, the vital signs (includes heart rate and respiratory rate) recorded at different time points will be summarized by treatment group and overall.

Any non-drug treatment procedures executed will also be summarized by treatment groups, system organ class and preferred term.

4.9 Determination of Sample Size

With 150 enrolled subjects per NmCV-5 arm and 75 subjects in the MenACWY-D arm, the study has a power of 80% to detect a 15.4% difference in proportion of subjects with severe solicited AEs reported within 7 days after any study vaccination between each NmCV-5 group and the MenACWY-D group, assuming the rate of severe reactions in the MenACWY-D group of 5%, a drop-out rate of 10%, and alpha of 0.05.

Power to show comparability of immune response in terms of the percentage of subjects with antibody titer greater than or equal to the cut-off level, based on various group sizes and equal expected underlying percentages, was done using one-sided Miettinen and Nurminen test and is provided in the protocol.

Assuming the expected proportion of subjects with antibody response greater than or equal to the cut-off (e.g. rSBA titer ≥ 8) is at least 95% for each of the vaccine serogroups in the NmCV-5 non-adjuvanted and MenACWY-D groups, then with 135 / 67 evaluable subjects per group, the study has power of 86% to demonstrate that the lower limit (LL) of 95% confidence interval (CI) for difference between the non-adjuvanted NmCV-5 group and MenACWY-D group is above -10% (commonly accepted non-inferiority margin) for each serogroup. With the same assumptions, the overall power to demonstrate that the lower limit (LL) of 95% confidence interval (CI) for difference between the non-adjuvanted NmCV-5 group and MenACWY-D group is above -10% for all serogroups would be at least 46%. See Table 4.9-1 for details

Table 4.9-1: Power to show comparability of immune response in terms of the percentage of subjects with antibody titer greater than or equal to the cut-off level, based on various group sizes and equal true underlying percentages

Expected percentage of subjects who achieve titers ≥ cut-off	Number of evaluable subjects per group	Power to demonstrate that the LL of 95% CI of the difference between groups is > -10% for an individual serogroup	Overall power to demonstrate that the LL of 95% CI of the difference between groups is > -10% for all serogroups
85%	120 vs. 60	47%	2%
	135 vs. 67	52%	4%
	150 vs. 75	56%	5%
90%	120 vs. 60	61%	8%
	135 vs. 67	65%	12%
	150 vs. 75	70%	17%
95%	120 vs. 60	81%	36%
	135 vs. 67	**86%**	**46%**
	150 vs. 75	89%	56%

Power to show that the ratio of rSBA Geometric Mean Titre (GMT) in the adjuvanted NmCV-5 group to that in the non-adjuvanted NmCV-5 group is at least 2 was calculated using a two-sample t-test according to different expected rSBA GMTs in the non-

adjuvanted NmCV-5 group and assumed standard deviations (SD) of log2-transferred rSBA titers and is provided in Table 4.9-2.

Table 4.9-2: Power to detect at least a 2-fold increase of rSBA GMTs after a 2-dose series with the adjuvanted NmCV-5 vs. non-adjuvantedNmCV-5, based on various group sizes and different assumed SD of log 2 rSBA titers

Expected rSBA GMTs in non-adjuvanted NmCV-5 group at 1 month post-Dose 2	Assumed SD of log2 rSBA titers	Number of evaluable subjects per group	Power to detect at least a 2-fold rSBA GMTs in adjuvanted NmCV-5 vs non-adjuvanted NmCV-5 for an individual serogroup	Overall power to detect at least a 2-fold rSBA GMTs in adjuvanted NmCV-5 vs non-adjuvanted NmCV-5 for all serogroups
500 to 1500 for various serogroups	1.5	150 vs. 150	>99%	> 99%
		135 vs. 135	>99%	> 99%
		120 vs. 120	>99%	> 99%
	2.0	150 vs. 150	99%	95%
		135 vs. 135	98%	92%
		120 vs. 120	97%	86%
	2.5	150 vs. 150	93%	70%
		135 vs. 135	**91%**	**61%**
		120 vs. 120	87%	50%
	3.0	150 vs. 150	82%	37%
		135 vs. 135	78%	29%
		120 vs. 120	73%	21%
	3.5	150 vs. 150	69%	16%
		135 vs. 135	65%	11%
		120 vs. 120	60%	8%

Assuming the true standard deviation of log2 rSBA titers is below than or equal to 2.5 for each of the five vaccine serogroups, with 135 evaluable subjects per group, the study has power of 91% to detect a 2-fold rSBA GMT increase in the adjuvanted NmCV-5 vs non-adjuvanted NmCV-5 for each serogroup. With the same assumptions, the overall power to detect a 2-fold rSBA GMT increase in the adjuvanted NmCV-5 vs non-adjuvanted NmCV-5 for all serogroups would be at least 61%.

4.10 Changes in the Conduct of the Study or Planned Analysis

For the logarithmic transformation of the titer results, logarithm based on 2 will be followed instead of base 10 as stated in the protocol.

5 REFERENCES

1. Miettinen, O., and Nurminen, M. 1985. Comparative analysis of two rates. Stat Med., 1985 Apr-Jun;4(2):213-26.

2. Farrington, C., and Manning, G 1990. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. Stat Med., Vol 9: 1447-1454

6 APPENDIX

Appendix 1. Miettinen and Nurminen Test

Miettinen and Nurminen (1985) proposed a test for testing whether the difference in proportions is equal to a specified non-zero value δ_0.

Suppose you have two populations from which dichotomous (binary) responses will be recorded. Random samples of and individuals are obtained from these two populations. The data from these samples can be displayed in a 2-by-2 contingency table as follows.

Group	Success	Failure	Total
Treatment	x_{11}	x_{12}	n_1
Control	x_{21}	x_{22}	n_2
Total	m_1	m_2	N

Say, we have the regular Maximum likelihood estimator (MLE's) $\hat{p}_1$ and $\hat{p}_2$ as

$$\hat{p}_1 = \frac{x_{11}}{n_1}, \hat{p}_2 = \frac{x_{21}}{n_2}$$

The estimates $\hat{p}_1$ and $\hat{p}_2$, are used in the numerator of the score statistics while MLE's $\tilde{p}_1$ and $\tilde{p}_2$, constrained so that $\tilde{p}_1 - \tilde{p}_2 = \delta_0$, are used in the denominator.

A correction factor of $N/(N\text{-}1)$ is applied to make the variance estimate less biased. The significance level of the test statistics is based on the asymptotic normality of the score statistics. The formula for computing this test statistic is

$$z_{MND} = \frac{\hat{p}_1 - \hat{p}_2 - \delta_0}{\hat{\sigma}_{MND}}$$

where

$$\hat{\sigma}_{MND} = \sqrt{\left[\frac{\tilde{p}_1\tilde{q}_1}{n_1} + \frac{\tilde{p}_2\tilde{q}_2}{n_2}\right]\left[\frac{N}{N-1}\right]}$$

$$\tilde{p}_1 = \tilde{p}_2 + \delta_0$$

$$\tilde{p}_1 = 2B\cos(A) - \frac{L_2}{3L_3}$$
$$A = \frac{1}{3}\left[\pi + \cos^{-1}\left(\frac{C}{B^3}\right)\right]$$
$$B = \sin(C)\sqrt{\frac{L_2^2}{9L_3^2} - \frac{L_1}{3L_3}}$$

$$C = \frac{L_2^3}{27L_3^3} - \frac{L_1 L_2}{6L_3^2} + \frac{L_0}{2L_3}$$

$$L_0 = x_{21}\delta_0(1-\delta_0)$$
$$L_1 = [N_2\delta_0 - N - 2x_{21}]\delta_0 + m_1$$
$$L_2 = (N+N_2)\delta_0 - N - m_1$$
$$L_3 = N, N = n_1 + n_2$$

Miettinen and Nurminen (1985) proposed inverting their score test to find the confidence interval. The lower limit is found by solving $z_{MND} = |z_{\alpha/2}|$ and the upper limit is the solution of $z_{MND} = -|z_{\alpha/2}|$.

NOTE: Except for a correction factor of $N/(N-1)$ that is applied to make the variance estimate ($\hat{\sigma}_{MND}$) less biased the Miettinen and Nurminen (1985) proposed test for differences in proportions equal to a specified non-zero value δ_0 is exactly same as that proposed by Farrington and Manning (1990). Adjusting the variance estimate proposed by Farrington and Manning (1990) by the correction factor will provide p-values and confidence intervals for testing difference between two proportions to specified non-zero value δ_0 as proposed by Miettinen and Nurminen (1985).

When δ_0 is zero, the test will be reduced to standard tests of null hypothesis of no difference between two proportions.

Appendix 2

Geometric Mean Titer (GMT)

The GMT will be calculated using the following formula:

$$\text{GMT} = 2^{\frac{\sum_{i=1}^{n}\log_2(t_i)}{n}}$$

where $t_1, t_2, \ldots, t_n$ are n observed immunogenicity titers.

Geometric Mean Ratio (GMR)

Geometric mean ratios measure the changes in immunogenicity titers within subjects.

The GMR will be calculated using the following formula:

$$\text{GMR} = 2^{\frac{\sum_{i=1}^{n} \log_2(v_{ij}/v_{ik})}{n}} = 2^{\frac{\sum_{i=1}^{n} \log_2(v_{ij}) - \log_2(v_{ik})}{n}}$$

where for n subjects, v_{ij} and v_{ik} are observed immunogenicity titers for subject i at time points j and k, $j \neq k$.

PAREXEL International Electronic Signature Page

This page is the manifestation of the electronic signature(s) used in compliance with PAREXEL International's electronic signature policies and procedures and in compliance with applicable regulations.

UserName: Liu, Tianzhe (liut2)
Title: Senior Biostatistician, GRO
Date: Friday, 17 August 2018, 01:41 AM GMT Standard Time
Meaning: Document contents authored.
==========

UserName: Kethireddypally, Rukmini (kethirr)
Title: Director, Biostatistician, GRO
Date: Friday, 17 August 2018, 04:06 AM GMT Standard Time
Meaning: Document contents approved.
==========

UserName: Kukutla, Ramakrishna (kukutlr)
Title: Principal Statistical Programmer, GRO
Date: Friday, 17 August 2018, 11:30 AM GMT Standard Time
Meaning: Document contents approved.
==========

UserName: Maiti, Kausik (maitik)
Title: Medical Director, GMS
Date: Wednesday, 29 August 2018, 07:29 AM GMT Standard Time
Meaning: Document contents approved.
==========

PAREXEL International

Serum Institute of India Private Limited (SIIPL); PATH

ACYWX-02 / CVIA058

A Phase 2, Observer-blind, Randomized, Controlled Study to Evaluate the Safety and Immunogenicity of Two Formulations of Investigational Meningococcal Groups ACYWX Conjugate Vaccine, Administered to Healthy Malian Children 12-16 Months of Age

Statistical Analysis Plan

PAREXEL Project Number: 233787

PAREXEL International

Sponsor Sign-Off

Title: 233787 Statistical Analysis Plan 20190213 v2.0			
Sponsor Project Number:	ACYWX-02/CVIA058	**PAREXEL Project Number:**	**233787**
Sponsor Name:	Serum Institute of India Private Limited (SIIPL) and Path		

SPONSOR Signatures

Signature below indicates that you have reviewed the document for clarity, completeness and consistency and approve it.

Signature 1:

Signature: Yuxiao Tang Date: April 1, 2019

Print Name: YUXIAO TANG Title: Senior Program officer

Signature 2:

Signature: Date: 03 April 2019

Print Name: Dr. Anil Chaudhari Title:

PAREXEL SIGNATURE PAGE

Signatures below confirm that the review process has been completed in accordance with SOP-GDO-WW-019.

This document has been approved and signed electronically on the final page by the following:

	Signatory
Author	Tuli De Project Role: Biostatistics Lead
	Signatory
Reviewer	Rukmini Kethireddypally Project Role: Biostatistics Reviewer

TABLE OF CONTENTS

RECORD OF MODIFICATIONS

Version Number	Effective Date	Author	Modification Details
0.1	26Apr2018	Kadiroo Jayaraman	New document
0.2	22May2018	Kadiroo Jayaraman	Corrections based on the comments by Rukmini
0.3	5Jun2018	Kadiroo Jayaraman	Corrections based on the comments by Rukmini
0.4	27Jun2018	Kadiroo Jayaraman	Corrections based on the comments from SIIPL/PATH
0.5	07Jul2018	Tianzhe Liu	Correction based on the comments from SIIPL/PATH
1.0	30Jul2018	Tianzhe Liu	Final version 1.0
2.0	15Nov2018	Tuli De	SAP Amendment for 1. changing Appendix section 6 for modification of MN CI method as proposed by sponsor statistician during blinded output review of Interim Analysis. The proposed method is compliant with SAS documentation of MN CI for non-inferiority. 2. A sentence has been added in section 4.7.3. (page 22) regarding non-availability of hSBA data

LIST OF ABBREVIATIONS

AE	Adverse event
ANOVA	Analysis of variance
CI	Confidence interval
CRF	Case report form
CRO	Contract research organization
DSMB	Data Safety Monitoring Board
EPI	Expanded Program on Immunization
FDA	Food and Drug Administration (US)
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
GMTs	Geometric mean titers
GMRs	Geometric mean ratios
IAP	Interim Analysis Plan
ICF	Informed consent form
IP	Investigational Product
IRB	Institutional review board
hSBA	Human complement serum bactericidal activity
MedDRA	Medical Dictionary for Regulatory Activities
NmCV-5	*Neisseria meningitidis* Groups ACYWX Conjugate Vaccine
PHE	Public Health England
PI	Principal Investigator
PT	Preferred term
RCDF	Reverse Cumulative Distribution Function
rSBA	Rabbit complement serum bactericidal activity
SAE	Serious adverse event
SBA	Serum bactericidal activity
SD	Standard deviation
SIIPL	Serum Institute of India Private Limited
SOC	System organ class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
TT	Tetanus toxoid
WHO	World Health Organization

1 INTRODUCTION

This study Statistical Analysis Plan (SAP) is applicable to both planned Interim Analysis (IA) and for the preparation of final study report after clinical database lock and unblinding.

As per study protocol, an IA including safety, reactogenicity and immunogenicity results (rSBA) at one month after the first vaccination (Day 28 Visit) will be performed; however, individual listings will not be generated at this point and any access to subject-level information about study groups will be masked. The statistical results that are relevant at Day 28 Visit will constitute IA results.

This study is designed to evaluate safety and immunogenicity of the non-adjuvanted and adjuvanted formulations of the investigational NmCV-5 vaccine in healthy children 12-16 months of age, in comparison with the licensed quadrivalent meningococcal conjugate vaccine (MenACWY-D; Menactra®). Menactra has been selected as an active control given the large safety database accumulated since the vaccine was introduced in the US in 2005, prequalified by WHO and progressively introduced in other countries. Both vaccines will be administered according to a 0, 3 month schedule to meningococcal vaccine-naïve healthy subjects.

This Statistical Analysis Plan (SAP) is based upon the following study documents:

- Study Protocol, Version 2.0 (August 11, 2017)
- Electronic Case Report Form (eCRF), Version 4.0 (November 27, 2017)

This document is in compliance with the requirements of the International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use guideline for Good Clinical Practice ICH E6 –GCP and ICH E9-Statistical Principles of Clinical Trials.

2 STUDY OBJECTIVES

Primary Objective:

1. To assess the reactogenicity of non-adjuvanted and adjuvanted formulations of NmCV-5 vaccine in comparison with the licensed MenACWY-D vaccine, as measured by the percentage of subjects with at least one severe solicited AE reported within 7 days after any vaccination.

Secondary Immunogenicity Objectives:

1. To assess immunogenicity of non-adjuvanted formulation of NmCV-5 vaccine in comparison with MenACWY-D vaccine, as measured by rSBA against serogroups A, C, W, Y and X at 1 month after the second vaccination.

2. To assess immunogenicity of adjuvanted formulation of NmCV-5 vaccine in comparison with non-adjuvanted formulation of NmCV-5 vaccine, as measured by rSBA against serogroups A, C, W, Y and X, at 1 month after the second vaccination.
3. To assess immune responses elicited by non-adjuvanted and adjuvanted formulations of NmCV-5 vaccine and MenACWY-D vaccine at 1 and 3 months after the first vaccination.

Secondary Safety Objective:

1. To evaluate the safety and reactogenicity of adjuvanted and non-adjuvanted formulations of NmCV-5 vaccine in healthy children, when compared to MenACWY-D.

Exploratory Objective:

1. To assess immunogenicity of adjuvanted and non-adjuvanted formulations of NmCV-5 vaccine and MenACWY-D vaccine, as measured by hSBA against serogroups A, C, W, Y and X at baseline, 1 month after the first vaccination and 1 month after the second vaccination (in a subset of subjects).
2. To further assess immunogenicity of adjuvanted and non-adjuvanted formulations of NmCV-5 vaccine and MenACWY-D vaccine, as measured by rSBA against serogroups A, C, W, Y, and X at baseline, 1, month and 3 months after the first vaccination and 1 month after the second vaccination.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a Phase 2, randomized, controlled, observer-blind, single-center study in healthy Malian children 12 to 16 months of age with three vaccination groups.

Duration of the study: The total study duration is approximately 6 months for each subject.

Data collection: Electronic Case Reporting Form (eCRF) and Home Visit Worksheets.

The study vaccination groups:

1. NmCV-5_non-adjuvanted group: approximately 150 subjects receiving the non-adjuvanted formulation of NmCV-5 vaccine at Visit Day 0 and Visit Day 84.

2. NmCV-5_adjuvanted group: approximately 150 subjects receiving the adjuvanted formulation of NmCV-5 vaccine at Visit Day 0 and Visit Day 84.

3. ACWY-D group: approximately 75 subjects receiving the licensed MenACWY-D (Menactra®) vaccine at Visit Day 0 and Visit Day 84.

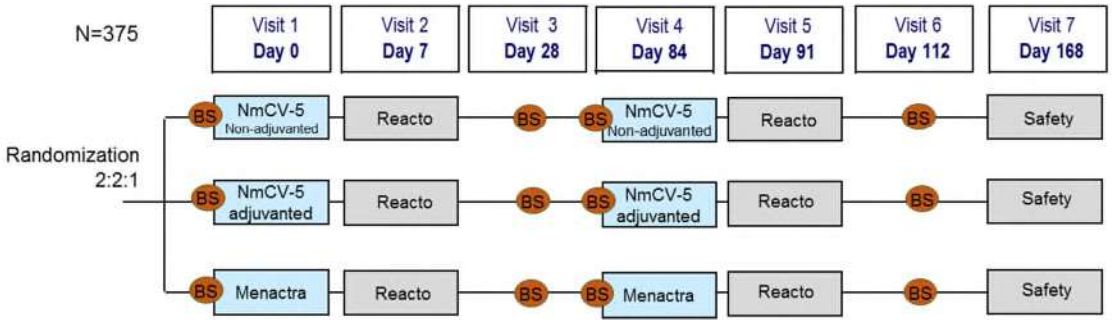
Randomization: At Visit Day 0, prior to the study vaccination, subjects will be randomized into the three study groups according to a 2:2:1 ratio

Vaccination Schedule: 0 and 3 months

Blood sample schedule: Four blood samples (approximately 5 mL each) at Visit 1 (Day 0, first vaccination), Visit 3 (Day 28), Visit 4 (Day 84, second vaccination) and Visit 6 (28 days after second vaccination).

Study visits: Seven visits at Day 0, Day 7, Day 28, Day 84, Day 91 (7 days post Dose 2), Day 112 (28 days post Dose 2) and Day 168 (84 days post Dose 2).

Figure 1. Study design



1. Notes: BS = Blood Sample
2. Written agreement to delay the MenAfriVac dose scheduled at 9 months of age: Prior to written informed consent, subject's parents/guardians may be asked to sign a pre-screening agreement as early as 9 months of age in order to delay the MenAfriVac dose until they can be considered for enrolment in the trial (trial subjects must be at least 12 months of age, have not received any meningococcal vaccines and have not received any vaccinations in the past 28 days).

3.2 Efficacy and Safety Variables

3.2.1 Primary reactogenicity endpoint:

1. Percentage of subjects with at least one severe solicited AE* within 7 days after first vaccination (Days 0-6).

   **Solicited AEs include tenderness, swelling/induration, irritability, drowsiness, decrease of eating, vomiting, and fever*

3.2.2 Secondary immunogenicity endpoints:

1. Percentage of subjects with rSBA titer ≥ 8 against serogroups A, C, W, Y and X at Visits Day 0, Day 28, Day 84 and Day 112.
2. Percentage of subjects with rSBA titer ≥ 128 against serogroups A, C, W, Y and X at Visits Day 0, Day 28, Day 84 and Day 112.

3. Percentage of subjects with fourfold rise in rSBA titers against serogroups A, C, W, Y and X at Visits Day 28 and Day 112.
    - For subjects with a pre-vaccination rSBA titer < 8, a post-vaccination titer of ⩾ 32;
    - For subjects with a pre-vaccination rSBA titer ⩾ 8, an increase in rSBA titer of at least 4 times the pre-vaccination titer.
4. rSBA Geometric Mean Titre (GMT) for serogroups A, C, W, Y and X at Visits Day 0, Day 28, Day 84 and Day 112.

3.2.3 Secondary safety endpoints:

1. Solicited local and systemic AEs reported within 7 days after each vaccination (Days 0-6 and Days 84-90);
2. Unsolicited AEs reported during 28 days after vaccination (Days 0-27 and Days 84-111);
3. AEs leading to premature withdrawal during the entire study period;
4. SAEs reported during the entire study period

3.2.4 Exploratory immunogenicity endpoints:

1. Percentage of subjects with hSBA titer ≥ 8 against serogroups A, C, W, Y and X at Visits Day 0, Day 28 and Day 112 (in a subset of subjects)
2. Percentage of subjects with hSBA seroresponse against serogroups A, C, W, Y and X at Visits Day 28 and Day 112 (in a subset of subjects), defined as:
    - for subjects with baseline hSBA titer < 4, post vaccination hSBA titer ≥ 8;
    - for subjects with baseline hSBA titer ≥ 4, an increase of at least four times the pre-vaccination hSBA
3. hSBA GMTs for serogroups A, C, W, Y and X at Visits Day 0, Day 28 and Day 112 (in a subset of subjects).
4. Percentage of subjects with rSBA titer ≥ 4, ≥ 16, ≥ 32, and ≥ 64 against serogroups A, C, W, Y and X at Visits Day 0, Day 28, Day 84 and Day 112.
5. Percentage of subjects with a fourfold increase in rSBA titers against serogroups A, C, W, Y and X at Visits Day 28 and Day 112 with the following criteria:
    - For subjects with a pre-vaccination rSBA titer < 4, a post-vaccination titer of ⩾ 16;
    - For subjects with a pre-vaccination rSBA titer ⩾ 4, a post-vaccination titer of at least 4 times the pre-vaccination titer.

6. Among subjects with a pre-vaccination rSBA titer ≥4, ≥8, ≥16, ≥ 32, ≥ 64, and ≥ 128, percentage of subjects with a post-vaccination titer of at least 4 times the pre-vaccination titer at Visits Day 28 and Day 112.

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard PAREXEL procedures.

The data for the planned IA with a data cut-off date as 7 Apr 2018 will be quality controlled as per applicable PAREXEL standard operating procedures. The data extraction will be set to appropriate date so that all data cleaning activities which includes any corrections to randomization numbers entered at site are taken care of.

4.2 General Considerations for Statistical Analysis and its Presentation

All statistical analyses will be performed using SAS® software Version 9.3 or later.

Medical history and Adverse Events (AE) will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). The frequency count and percentage of subjects will be summarized according to the coded terms of system organ class (SOC) and preferred term. Subject-wise data listing will be provided.

Using the World Health Organization Drug Dictionary (WHO DD), prior and concomitant medications will be tabulated by drug classification, preferred drug name and study group.

Continuous data will also be summarized in terms of the descriptive statistics, number of observations (n), mean, SD, median, minimum, and maximum, unless otherwise stated.

Continuous data that are expected to be skewed will be presented in terms of the maximum, upper quartile, median, lower quartile, minimum and number of observations. The mean, median will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarized in terms of the number of subjects providing data at the relevant time point (N), frequency counts and percentages.

Percentages will be presented to one decimal place. Percentages will be provided even for zero counts. Percentages will be calculated using N as the denominator.

A p-value greater than or equal to 0.001, in general, will be presented to three decimal places, while p-values less than 0.001 will be presented as "<0.001".

Confidence intervals will be presented to one more decimal place than the raw data.

Visit and Observation period Labeling

In tables, listings and figures, visits and observation periods will be labeled using minutes/days up to and including Day 112. Specifically,

Day 0, 30-minutes, Days 0-6, Days 0-27, Days 84-90, Days 84-111, Day 28, Day 84, and Day 112.

All baseline summaries will be presented using label Day 0 (Baseline).

4.3 Study Subjects

4.3.1 Disposition of Subjects

The number of subjects whose parents signed an agreement to defer immunization with MenAfriVac, the number of these subjects subsequently enrolled and the number of subjects who subsequently received MenAfriVac from those not enrolled will be presented. The number of subjects screened, screen failed, eligible, randomized, vaccinated and discontinued will be summarized overall and by vaccination group, as applicable. Subjects who discontinued from the study will also be summarized by reasons for discontinuation as provided in eCRF. A listing of the subject disposition/end of study record for all subjects who discontinued the study prematurely will be produced.

A summary of the number and percentage of subjects who completed, discontinued or had delay in the planned course of study vaccination and the primary reason(s) for discontinuation/delay of study vaccination will be provided. Reasons for study vaccination discontinuation/delay will be presented in the order they are displayed in the eCRF. A listing for study vaccination discontinuation/delay will also be generated by vaccination groups.

Disposition summaries will be based on enrolled population.

4.3.2 Protocol Deviations

Major protocol deviations are defined as those deviations from the protocol that are likely to have an impact on the subject's rights, safety, well-being, and/or on the validity of the data for analysis. This will include all those deviations to be reported in the clinical study report (CSR).

In the event that a subject is allocated the incorrect study treatment as per the study randomization list, it will be considered as a protocol deviation.

The number of subjects with protocol deviations will be summarized by category (Major or Minor) and deviation classification overall and by vaccination group. Protocol deviations will be listed with date and study day of occurrence, deviation category, deviation description and analysis populations from which subject is excluded.

The number of subjects included in each analysis population will be summarized. A listing of subjects included in each analysis population will also be provided. Subject exclusion from analysis sets will be listed with reasons for exclusions.

Above summaries will be based on Exposed population.

4.4 Analysis Populations

Enrolled Population:

All screened subjects who provide informed consent and received a subject ID, regardless of the subject's randomization and treatment status in the trial.

Exposed Population:

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

Immunogenicity Populations:

Immunogenicity analyses will be performed on both the Full Analysis (FA) Population and Per Protocol (PP) Population.

Full Analysis Population

All subjects in the enrolled population who were randomized, received a study vaccination, and provide an evaluable serum sample at least at one time point post-vaccination.

The analysis based on this population will serve as supportive results for all secondary immunogenicity objectives. Subjects in the FA population will be analyzed "as randomized" (i.e., according to the vaccine a subject was designated to receive, which may be different from the vaccine the subject actually received).

Per Protocol Population

All subjects in the FA Population who correctly received two doses of study vaccine per randomization with no major protocol violations that are determined to potentially interfere with the immunogenicity assessment of the study vaccines. This population will serve as the primary analysis population for all immunogenicity objectives.

Due to unpredictability of some irregularities, the criteria for exclusion of subjects from the Per Protocol Population will be determined before the database is locked and will be based on the blinded review of protocol violations.

Safety Population:

All subjects in the enrolled population who received a study vaccination and had any safety data available.

Subjects will be analyzed as "treated" (i.e., according to the actual vaccine received at the first dose). All safety analyses will be performed using this population. The denominators for different safety endpoints may vary according to the number of subjects with available data for the specific endpoint. For example, the solicited adverse event endpoints will be based only on those who have the corresponding CRF data regardless of other safety follow-up data.

Decisions regarding the exclusion of subjects and/or subject data from analyses will be made prior to unblinding during blinded data review meeting and will be documented and approved by the SIIPL/PATH.

4.5 Demographic and Other Baseline Characteristics

4.5.1 Demographics and Baseline Characteristics

Descriptive statistics (number of subjects, mean, standard deviation, median, minimum and maximum) for age, length and weight at enrolment will be calculated by overall and by vaccine group. Distributions of subjects by gender, race and ethnicity will be summarized (using counts and percentages) overall and by vaccine group. Baseline characteristics include vital signs, temperature, heart rate, and respiratory rate. Baseline characteristics will be listed and summarized (number of subjects, mean, standard deviation, median, minimum and maximum).

Demographic summaries will be based on enrolled population who are randomized.

4.5.2 Medical History

Medical conditions will be coded by the medical dictionary for regulatory activities (MedDRA). The final MedDRA version to be used will be decided prior to database lock.

Medical conditions present at screening will be summarized and listed. They will be summarized by SOC and preferred term. These will be based on exposed population.

4.5.3 Prior and Concomitant Therapies

Prior and concomitant therapies will be coded by World Health Organization – Drug Dictionary (WHOB2B3HERBAL Dictionary).

4.5.3.1 Prior Medications and Vaccines

The following are considered prior medications for this study:

- any investigational or non-registered product (drug or vaccine) received prior to enrolment;
- any vaccine administered prior to enrolment;
- any immunosuppressant or other immune-modifying drug including systemic steroids, within 3 months prior to enrolment;
- any blood, blood product and/or plasma derivative or any parenteral immunoglobulin preparation within 3 months prior to enrolment;
- any systemic antibiotic within 3 days prior to enrolment;
- Any antipyretic/analgesic within 24 hours prior to first vaccination.

If above medications were administered to the subject within the specified window prior to the first study vaccination, they will be recorded on the Concomitant Medications page of eCRF.

Prior medications and vaccines will be listed and summarized. They will be summarized by generic preferred name, and Anatomical Therapeutic Chemical (ATC) class. More than one ATC class per medication is possible and the medication will be reported under all applicable classes. A subject with multiple occurrences within a ATC class is counted only once for that ATC class; similarly a subject with multiple occurrences within a generic preferred name, is counted only once.

4.5.3.2 Concomitant Medications, Vaccines, Non-drug Treatment and Procedures

Medications taken at any time during the study period are considered as concomitant medications and will be summarized by vaccination group in the exposed population.

Concomitant medications and vaccines will be listed and summarized similar to Prior medications.

The non-drug treatment and procedures captured in eCRF will be listed and summarized. They will be summarized by System Organ Class (SOC) and preferred term.

Prophylactic Antipyretics / Analgesics

Medications taken for prophylaxis are those administered in the absence of any symptom and intended to prevent the onset of post-vaccination symptoms. Medications taken for treatment are intended to reduce or eliminate the symptoms that are present.

The antipyretics and/or analgesic medications taken within 24 hours prior to the study vaccination recorded in eCRF will be listed and summarized.

The antipyretics / analgesics administered after study vaccination and the reason for their use (prophylaxis versus treatment) will be listed and summarized based on recorded data in source documents and Concomitant Medications eCRF.

4.6 Treatment Compliance

No treatment compliance measures are included in this study.

4.7 Efficacy Evaluation

4.7.1 Analysis and Data Conventions

The primary objective is to evaluate the reactogenicity of adjuvanted and non-adjuvanted formulations of NmCV-5 vaccine in comparison with the licensed comparator (Menactra®). The secondary objectives are to assess safety and the immune response of adjuvanted and non-adjuvanted formulations of NmCV-5 vaccine.

4.7.1.1 Multi-center Studies

The study is conducted in a single center.

4.7.1.2 Adjustments for Covariates

No analysis specified includes adjustment for covariates.

4.7.1.3 Handling of Dropouts or Missing Data

Missing data will not be imputed and will be analyzed as if they were randomly missing.

The number and percentage of subjects with missing data for the primary and secondary endpoints will be summarized by treatment group and overall.

4.7.1.4 Multiple Comparisons/Multiplicity

Due to hypothesis generating nature of this study, all statistical comparisons for reactogenicity, safety, and immunogenicity endpoints will be carried out without an adjustment for multiple comparisons. All statistical tests except for non-inferiority will be two-sided with a type I error rate of 5%. Non-inferiority tests will be one-sided with type I error of 2.5%. The 95% confidence interval will be presented for estimates as described later.

4.7.1.5 Interim Analyses

An interim analysis including safety, reactogenicity and immunogenicity results (rSBA) at 1 month after the first vaccination will be performed. Individual listings will not be generated at this point and any access to subject-level information about study groups will be masked.

The objective of Interim Analysis (IA) is to compare treatment groups one month post first vaccination with respect to the immunogenicity responses so as to make a choice among the two NmCV-5 formulations for use in future clinical development. Comparisons with regard to safety and reactogenicity also will be performed, as applicable.

For presentation of IA immunogenicity summary results, table layouts will be generated in such a way that study blind is broken only at the treatment (i.e., vaccine) group level, but there shall not be any subject level unblinding. The study disposition, protocol deviation, demographic, and safety data will also be presented by group level; however, unlike the immunogenicity results, the treatment (i.e., vaccine) *per se* will not be identified and the groups will be labelled Vaccine 1, 2, and 3. Moreover, no actual subject numbers will be presented, neither numerators nor denominators, and only percentages will be presented for individual groups. This process will help minimize any potential subject-level unblinding. Individual subject listings will be generated for purposes of statistical quality control and will not be circulated to any blinded members at PAREXEL, sponsor or site.

Where possible, IA results will use table layouts that can be included in final study ICH E3 Clinical Study Report.

Database soft-lock has to be achieved on the data to be used for IA after cleaning. An IA snapshot of the database along with IA results will be stored in password protected area within statistical reporting systems of PAREXEL until final database lock and unblinding is achieved.

The interim analysis results will only be circulated to pre-specified representatives of SIIPL and PATH and will not be circulated to the Investigators or any other site staff.

4.7.1.6 Examination of Subgroups

No subgroup analysis is planned for this study.

4.7.2 Statistical Methods for Primary Objective

Precision estimates of the percentages of subjects with at least one severe solicited AE reported within 7 days after any vaccination will be computed by vaccine group using the two-sided 95% Clopper-Pearson confidence intervals.

The differences between groups (Group NmCV-5_non-adjuvanted - Group MenACWY-D and Group NmCV-5_adjuvanted - Group MenACWY-D) in the percentages of subjects with at least one severe solicited AE reported within 7 days after any vaccination will be provided along with their two-sided 95% CIs obtained by the Miettinen and Nurminen method. The details of the Miettinen and Nurminen method are provided in the Appendix 1.

4.7.3 Statistical Methods for Secondary Objectives

4.7.3.1 Analysis of Secondary Immunogenicity Objectives

For all rSBA titers reported as "<4" will be treated as "2" in immunogenicity analysis.

Per protocol population will be used as primary analysis population for assessing immunogenicity objectives.

Supportive analyses of immunogenicity objectives will be based on full analysis population.

Proportion of subjects with antibody response greater than or equal to the cut-off (e.g. rSBA titer ≥ 8 or 128) at Visits Day 0, Day 28, Day 84 and Day 112 and proportion of subjects with four-fold increase from baseline at Visits Day 28 and 112.

For each *N. meningitidis* serogroup A, C, W, Y, and X the percentages of subjects with rSBA titers ≥ 8 and the corresponding exact two-sided 95% CIs based on Clopper-Pearson method will be calculated for each study group at baseline (Day 0), one and three months after the first vaccination (Day 28 Visit, Day 84 Visit) and one month after the second vaccination (Day 112 Visit).

Similar calculations will be repeated with cutoff of rSBA titers ≥ 128.

For each of N. *meningitidis* serogroup A, C, W, Y, and X the percentages of subjects with four-fold rise (for subjects with a pre-vaccination rSBA titer < 8, a post-vaccination titer of ⩾ 32; for subjects with a pre-vaccination rSBA titer ⩾ 8, an increase in rSBA titer of at least 4 times the pre-vaccination titer) in post vaccination rSBA titers from baseline and the corresponding exact two-sided 95% CIs based on the Clopper-Pearson method will be calculated for each study group at one month after the first vaccination (Day 28 Visit) and one month after the second vaccination (Day 112 Visit).

At Day 112 Visit and for each of N. *meningitidis* serogroup A, C, W, Y, and X, and for each rSBA titer ≥ cut-off (8,128), the difference in percentages between NmCV-5 non-adjuvanted group and MenACWY-D group and between NmCV-5 non-adjuvanted group and NmCV-5 adjuvanted group will be provided along with the two-sided 95% CIs that will be constructed using the method of Miettinen and Nurminen. Similar comparisons will be provided between NmCV-5 adjuvanted group and MenACWY-D group at Day 112

Visit. Similar analysis will be repeated at Day 28 and Day 84 Visits. At Day 28 and 112 Visits, similar comparisons will be provided for four-fold rise in post vaccination rSBA.

Let P_{NNSG}, P_{NASG} and P_{MNSG} represent the corresponding percentages of subjects with rSBA titers ≥ 8 for a given serogroup for NmCV-5 non-adjuvanted, NmCV-5 adjuvanted and MenACWY-D groups, respectively. We will test the following hypotheses,

H_{01}: P_{NNSG}-P_{MNSG} ≤ -10% versus H_{a1}: P_{NNSG}-P_{MNSG} > -10%
H_{02}: P_{NNSG}-P_{NASG} ≤ -10% versus H_{a2}: P_{NNSG}-P_{NASG} > -10%

We can form similar hypotheses for the case of rSBA titers ≥ 128 and four-fold rises.

At one month post second vaccination (Day 112 Visit), for a given titer cut-off, if the lower limit (LL) of 95% confidence interval (CI) for difference in percentages between NmCV-5 non-adjuvanted group and MenACWY-D group or between between NmCV-5 non-adjuvanted group and NmCV-5 adjuvanted group is above -10% (commonly accepted non-inferiority margin) for each serogroup A, C, W, Y, and X then non-inferiority of NmCV-5 non-adjuvanted group to MenACWY-D group or NmCV-5 non-adjuvanted group to NmCV-5 adjuvanted group will be demonstrated for each corresponding endpoint, respectively. Similar comparisons will be provided between NmCV-5 adjuvanted group and MenACWY-D group. Similar analysis will be repeated at one month post first vaccination (Day 28 Visit).

rSBA GMT for serogroups A, C, W, Y and X at Visits Day 0, Day 28, Day 84 and Day 112.

The rSBA titers at each visit (Day 0, Day 28, Day 84, and Day 112) for each study group will be logarithmically transformed (base 2) to fulfil the normal distribution assumption. For each study group, *N. meningitidis* serogroup (A, C, W, Y, and X) at each visit Day 0, Day 28, Day 84, and Day 112, the GMTs will be calculated with their associated two-sided 95% CIs, by exponentiating the corresponding log-transformed means and their 95% CIs.

For each study group, *N. meningitidis* serogroup (A, C, W, Y, and X) at each post vaccination visit Day 28, Day 84, and Day 112, the logarithmically transformed rSBA change from baseline (Day 0) will be obtained. The Geometric Mean Ratio (GMR: post vaccination/baseline) will be calculated with their associated two-sided 95% CIs, by exponentiating the corresponding log-transformed means and their 95% CIs.

For each of the five vaccine serogroups at Day 112 Visit, the comparison of GMTs and GMRs will be made using one-way analysis of variance (ANOVA) containing term for vaccine group, with the logarithmically transformed rSBA titres as a dependent variable. Similar analysis will be repeated at Day 28 and Day 84 Visits.

The ratio of GMTs between the study vaccination groups and the corresponding 95% CIs will be constructed by exponentiating the mean difference and the confidence limits in log2 (titer) obtained within ANOVA. Similarly, the logarithmically transformed rSBA change

from baseline will be analysed using ANOVA to obtain ratio of GMRs and their associated 95% CIs.

In addition, a reverse cumulative distribution plot of each immunogenicity measure will be created. Reverse cumulative distribution function (RCDF) refers to the complement of cumulative distribution function given by the following function.

$$\text{RCDF} = 1 - \text{CDF} = 1 - \int_{-\infty}^{x} f(x)dx$$

RCDF will be generated for all the immunogenicity measures for each serogroup by treatment group. Empirical RCDF will be generated for each titer measure and superimposed in graphs with similar values based on lognormal function. Cutoff points of 8 and 128 indicated in the graphs.

4.7.3.2 Statistical Methods for Exploratory Immunogenicity Objective

Exploratory immunogenicity endpoints w.r.t rSBA titer

(a) Percentage of subjects with rSBA titer ≥ 4, ≥ 16, ≥ 32, and ≥ 64 against serogroups A, C, W, Y and X at Visits Day 0, Day 28, Day 84 and Day 112

(b) Percentage of subjects with a fourfold increase in rSBA titers against serogroups A, C, W, Y and X at Visits Day 28 and Day 112 with the following criteria:

- For subjects with a pre-vaccination rSBA titer < 4, a post-vaccination titer of ⩾ 16;
- For subjects with a pre-vaccination rSBA titer ⩾ 4, a post-vaccination titer of at least 4 times the pre-vaccination titer.

(c) Among subjects with a pre-vaccination rSBA titer ≥4, ≥8, ≥16, ≥ 32, ≥ 64, and ≥ 128, percentage of subjects with a post-vaccination titer of at least 4 times the pre-vaccination titer at Visits Day 28 and Day 112.

For each N. meningitidis serogroup the percentages of subjects with rSBA ≥4, ≥16, ≥ 32, and ≥ 64 and the corresponding exact two-sided 95% CIs based on Clopper-Pearson method will be calculated for each study group at baseline (Day 0), one (Day 28 Visit) and three months (Day 84 Visit) after the first vaccination and one month after the second vaccination (Day 112 Visit).

Percentages of subjects with four-fold rSBA titer rise with criteria described in exploratory immunogenicity endpoints for rSBA and the corresponding exact two-sided 95% CIs based on the Clopper-Pearson method against these serogroups will be calculated for each study group at one month after the first vaccination (Day 28 Visit) and one month after the second vaccination (Day 112 Visit).

Exploratory Immunogenicity endpoints related to hSBA titer:

Whenever the hSBA testing is performed and the results available, the analyses related to corresponding exploratory endpoints will be performed as follows,

(a) Percentage of subjects with hSBA titer ≥ 8 against serogroups A, C, W, Y and X at Visits Day 0, Day 28 and Day 112 (in a subset of subjects)

(b) Percentage of subjects with hSBA seroresponse against serogroups A, C, W, Y and X at Visits Day 28 and Day 112 (in a subset of subjects), defined as:

- for subjects with baseline hSBA titer < 4, post vaccination hSBA titer ≥ 8;

- for subjects with baseline hSBA titer ≥ 4, an increase of at least four times the pre-vaccination hSBA

(c) hSBA GMTs for serogroups A, C, W, Y and X at Visits Day 0, Day 28 and Day 112 (in a subset of subjects).

For each *N. meningitidis* serogroup the percentages of subjects with hSBA titers ≥ 8 and the corresponding exact two-sided 95% CIs based on Clopper-Pearson method will be calculated for each study group at baseline (Day 0), one month after the first vaccination (Day 28) and one month after the second vaccination (Day 112).

Percentages of subjects with hSBA seroresponse and the corresponding exact two-sided 95% CIs based on the Clopper-Pearson method against these serogroups will be calculated for each study group at one month after the first vaccination (Day 28) and one month after the second vaccination (Visit Day 112).

Post vaccination at Day 28 and Day 112 Visits, for each of N. *meningitidis* serogroup A, C, W, Y, and X, and for each of hSBA endpoints (a) & (b), the difference in percentages between each of the NmCV-5 (adjuvanted and non-adjuvanted) groups and MenACWY-D group as well as between the adjuvanted and non-adjuvanted NmCV-5 groups will be provided along with the two-sided 95% CIs that will be constructed using the method of Miettinen and Nurminen.

For each *N. meningitidis* serogroup, the hSBA titers at each visit (Days 0, 28, 112) for each study group will be logarithmically transformed (base2) to fulfil the normal distribution assumption.

The ratio of GMTs between each of the NmCV-5 (adjuvanted and non-adjuvanted) groups and MenACWY-D group as well as between the adjuvanted NmCV-5 vs non-adjuvanted NmCV-5 study groups and the corresponding 95% CIs will be constructed by exponentiating the mean difference and the confidence limits in log2 (titer) obtained within ANOVA. Similarly the logarithmically transformed hSBA change from baseline will be analysed using ANOVA to obtain ratio of GMRs (post vaccination / baseline) and their associated 95% CIs.

In addition, a reverse cumulative distribution plot of each measure will be created.

These analyses were planned to be performed based on availability of hSBA data. As no data on hSBA titer is available, no outputs will be produced for hSBA titer data as part of exploratory endpoint analysis.

A by-subject listing of immunogenicity assessment at Day 0 baseline, Day 28, Day 84 and Day 112 will be provided.

4.7.3.3 Secondary Safety Objectives

The design of the study allows a comparison among groups after each vaccination and after any vaccination. All solicited adverse events will be summarized according to defined severity grading scales.

Analysis of Solicited Adverse Events

All solicited adverse events will be summarized according to defined severity grading scales. Frequencies and percentages of subjects experiencing each adverse event will be presented for each symptom severity. Summary tables showing the occurrence of any local or systemic adverse event will also be presented.

The difference between groups (Group NmCV-5_non-adjuvanted - Group MenACWY-D and Group NmCV-5_adjuvanted - Group MenACWY-D) in percentage of subjects with at least one local or systemic adverse event overall and at each time point will be calculated along with their two-sided 95% CIs obtained using the Miettinen and Nurminen method.

Post-vaccination solicited adverse events reported from Day 0 to Day 6 will be summarized by severity and by vaccine group. Separate analysis will be performed for solicited AEs reported 30 minutes after vaccination. All the solicited reactions occurring up to 7 days after each vaccination will be summarized according to severity grading based on the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events provided in Appendix II of the protocol.

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

Use of antipyretics and analgesics will be summarized by frequency, by type of use (prophylactic versus treatment) and percentage of subjects reporting use.

Body temperature will be summarized separately according to the 2 schemes described below.

Temperature schemes.

- by 0.5 °C increments from 36.0°C up to ≥40°C

- <36.0, ≥36.0-<37.0, ≥37.0-<38.0, ≥ 38.0-<39.0, ≥39.0-<40, ≥40°C

Analysis of Unsolicited Adverse Events

All the adverse events occurring during the study, judged either as related, or not related to vaccination by the investigator, will be recorded.

The original verbatim terms used by investigators to identify adverse events in the eCRFs will be mapped to preferred terms using the MedDRA dictionary. The adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class. All reported adverse events, including adverse events judged by the investigator as related to study vaccine, will be summarized according to system organ class and preferred term within system organ class. When an adverse event occurs more than once for a subject, it will be considered as multiple events and each event will be presented distinctly.

The summaries will be presented by period of onset and will include frequency distributions of the different adverse events:

- All unsolicited AEs reported within 28 days after each vaccination;
- AEs leading to premature withdrawal from the study during the entire study period;
- SAEs reported during the entire study period.

The analysis of unsolicited adverse events comprises the following categories:

- Any unsolicited AEs;
- Related unsolicited AEs (by causality);
- Unsolicited AE by Outcome;
- SAEs;
- Related SAEs;
- Unsolicited AEs leading to withdrawal from the study;
- Unsolicited AEs leading to withdrawal from study vaccination but remaining in the study;
- Unsolicited AEs leading to hospitalization;
- Any AEs leading to death.

Data listings of all adverse events will be provided by subject.

- For IA details of safety endpoints see Section 4.7.1.5

4.8 Safety Evaluation

Safety evaluation forms the secondary objectives in this study and is already discussed in section 4.7.3.3.

4.8.1 Extent of Exposure

The number and percentage of randomized subjects who completed the planned course of study vaccination will be summarized by study day, vaccination group and overall. The number and percentage of subjects who discontinued from the study vaccination will also be summarized by study day, vaccination group and overall.

These summaries will be provided for the exposed population.

4.8.2 Adverse Events

The reporting of adverse events is already discussed in section 4.7.3.3. Some additional information is given in the following.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1 or later. If a subject experiences an adverse event more than once, the event at the most severe occurrence will be considered. However, the number of events occurred will also be included in the summary tables. Subjects will be included only once in the total for a body system where they experienced one or more events.

Adverse event summaries will be ordered in terms of decreasing frequency for System Organ Class (SOC), and Preferred Term (PT) within SOC for all the vaccine groups and then alphabetically for SOC, and PT within SOC.

For each subject and each adverse event, the worst severity recorded will be attributed and used in the by-severity summaries. Similarly, the worst causality (most related to treatment) will be attributed and used in the by-causality summaries. If severity or causality is missing, the worst case will be assumed. Where multiple recordings of the same event are recorded, the number of such events will be tabulated.

A summary of the number of subjects with Treatment Emergent Adverse Event (TEAE) outcome into “Not recovered/Not resolved”, “Recovered/Resolved”, “Recovered/Resolved with sequelae/resolved with sequelae”, “Recovering/Resolving (ongoing)”, “Fatal”, and “Unknown” categories for number of events by treatment group will be provided. (Analysis set: Safety Set).

4.8.3 Deaths, Serious Adverse Events, and Other Significant Adverse Events

Deaths and SAEs will be summarized by treatment group including severity, relatedness and seriousness criteria.

4.8.4 Clinical Laboratory Evaluation

This study has no safety laboratory measurements.

4.8.5 Vital Signs, Physical Findings and Other Observations Related to Safety

Other than temperature, the vital signs (includes heart rate and respiratory rate) recorded at different time points will be summarized by treatment group and overall.

Any non-drug treatment procedures executed will also be summarized by treatment groups, system organ class and preferred term.

4.9 Determination of Sample Size

With 150 enrolled subjects per NmCV-5 arm and 75 subjects in the MenACWY-D arm, the study has a power of 80% to detect a 15.4% difference in proportion of subjects with severe solicited AEs reported within 7 days after any study vaccination between each NmCV-5 group and the MenACWY-D group, assuming the rate of severe reactions in the MenACWY-D group of 5%, a drop-out rate of 10%, and alpha of 0.05.

Power to show comparability of immune response in terms of the percentage of subjects with antibody titer greater than or equal to the cut-off level, based on various group sizes and equal expected underlying percentages, was done using one-sided Miettinen and Nurminen test and is provided in the protocol.

Assuming the expected proportion of subjects with antibody response greater than or equal to the cut-off (e.g. rSBA titer ≥ 8) is at least 95% for each of the vaccine serogroups in the NmCV-5 non-adjuvanted and MenACWY-D groups, then with 135 / 67 evaluable subjects per group, the study has power of 86% to demonstrate that the lower limit (LL) of 95% confidence interval (CI) for difference between the non-adjuvanted NmCV-5 group and MenACWY-D group is above -10% (commonly accepted non-inferiority margin) for each serogroup. With the same assumptions, the overall power to demonstrate that the lower limit (LL) of 95% confidence interval (CI) for difference between the non-adjuvanted NmCV-5 group and MenACWY-D group is above -10% for all serogroups would be at least 46%. See Table 4.9-1 for details

Table 4.9-1: Power to show comparability of immune response in terms of the percentage of subjects with antibody titer greater than or equal to the cut-off level, based on various group sizes and equal true underlying percentages

Expected percentage of subjects who achieve titers ≥ cut-off	Number of evaluable subjects per group	Power to demonstrate that the LL of 95% CI of the difference between groups is > -10% for an individual serogroup	Overall power to demonstrate that the LL of 95% CI of the difference between groups is > -10% for all serogroups
85%	120 vs. 60	47%	2%

	135 vs. 67	52%	4%
	150 vs. 75	56%	5%
90%	120 vs. 60	61%	8%
	135 vs. 67	65%	12%
	150 vs. 75	70%	17%
95%	120 vs. 60	81%	36%
	135 vs. 67	**86%**	**46%**
	150 vs. 75	89%	56%

Power to show that the ratio of rSBA Geometric Mean Titre (GMT) in the adjuvanted NmCV-5 group to that in the non-adjuvanted NmCV-5 group is at least 2 was calculated using a two-sample t-test according to different expected rSBA GMTs in the non-adjuvanted NmCV-5 group and assumed standard deviations (SD) of log2-transferred rSBA titers and is provided in Table 4.9-2.

Table 4.9-2: Power to detect at least a 2-fold increase of rSBA GMTs after a 2-dose series with the adjuvanted NmCV-5 vs. non-adjuvantedNmCV-5, based on various group sizes and different assumed SD of log 2 rSBA titers

Expected rSBA GMTs in non-adjuvanted NmCV-5 group at 1 month post-Dose 2	Assumed SD of log2 rSBA titers	Number of evaluable subjects per group	Power to detect at least a 2-fold rSBA GMTs in adjuvanted NmCV-5 vs non-adjuvanted NmCV-5 for an individual serogroup	Overall power to detect at least a 2-fold rSBA GMTs in adjuvanted NmCV-5 vs non-adjuvanted NmCV-5 for all serogroups
500 to 1500 for various serogroups	1.5	150 vs. 150	>99%	> 99%
		135 vs. 135	>99%	> 99%
		120 vs. 120	>99%	> 99%
	2.0	150 vs. 150	99%	95%
		135 vs. 135	98%	92%
		120 vs. 120	97%	86%
	2.5	150 vs. 150	93%	70%
		135 vs. 135	**91%**	**61%**
		120 vs. 120	87%	50%
	3.0	150 vs. 150	82%	37%
		135 vs. 135	78%	29%
		120 vs. 120	73%	21%
	3.5	150 vs. 150	69%	16%
		135 vs. 135	65%	11%
		120 vs. 120	60%	8%

Assuming the true standard deviation of log2 rSBA titers is below than or equal to 2.5 for each of the five vaccine serogroups, with 135 evaluable subjects per group, the study has power of 91% to detect a 2-fold rSBA GMT increase in the adjuvanted NmCV-5 vs non-adjuvanted NmCV-5 for each serogroup. With the same assumptions, the overall power to detect a 2-fold rSBA GMT increase in the adjuvanted NmCV-5 vs non-adjuvanted NmCV-5 for all serogroups would be at least 61%.

4.10 Changes in the Conduct of the Study or Planned Analysis

For the logarithmic transformation of the titer results, logarithm based on 2 will be followed instead of base 10 as stated in the protocol.

5 REFERENCES

1. Miettinen, O., and Nurminen, M. 1985. Comparative analysis of two rates. Stat Med., 1985 Apr-Jun;4(2):213-26.

2. Farrington, C., and Manning, G 1990. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. Stat Med., Vol 9: 1447-1454

3. SAS support link of Miettinen and Nurminen CI: http://support.sas.com/documentation/cdl/en/procstat/67528/HTML/default/viewer.htm#procstat_freq_details53.htm#procstat.freq.freqrdiffexact

6 APPENDIX

Appendix 1. Miettinen and Nurminen(Score) confidence Limits

Suppose we have two populations from which dichotomous (binary) responses will be recorded. Random samples of and individuals are obtained from these two populations. The data from these samples can be displayed in a 2-by-2 contingency table as follows.

Group	Success	Failure	Total
Treatment	x_{11}	x_{12}	n_1
Control	x_{21}	x_{22}	n_2
Total	m_1	m_2	N

Say, we have the regular Maximum likelihood estimator (MLE's) $\hat{p}_1$ and $\hat{p}_2$ as

$$\hat{p}_1 = \frac{x_{11}}{n_1}, \hat{p}_2 = \frac{x_{21}}{n_2}$$

The Miettinen and Nurminen confidence limits for risk difference (Miettinen and Nurminen 1985) are computed by inverting score tests for the risk difference. A score-based test statistic for the null hypothesis that the risk difference equals δ can be expressed as –

$$T(\delta) = (\hat{\delta} - \delta)/\sqrt{\widetilde{Var}(\delta)}$$

Where $\hat{d}$ is the observed value of the risk difference ($\widehat{p_1} - \widehat{p_2}$).

$$\widetilde{Var}(\delta) = \left(\frac{n}{n-1}\right)\left(\frac{\widetilde{p_1}(\delta)\left(1-\widetilde{p_1}(\delta)\right)}{n_1} + \frac{\widetilde{p_2}(\delta)\left(1-\widetilde{p_2}(\delta)\right)}{n_2}\right)$$

And $\widetilde{p_1}(\delta)$ and $\widetilde{p_2}(\delta)$ are the maximum likelihood estimates of the row 1 and row 2 risks (proportions) under the restriction that the risk difference is δ.

The 100(1-α) % confidence interval for the risk difference consisits of all values of δ for which the score test statistics T(δ) falls in the acceptance region $\{\delta: T(\delta) < z_{\alpha/2}\}$ where $z_{\alpha/2}$ is the 100(1- α /2) percentile of the standard normal distribution.

A correction factor of n/(n-1) is applied to make the variance estimate $\widetilde{Var}(\delta)$ less biased.

The maximum likelihood estimates of p_1 and p_2 , subject to the constraint that the risk difference is δ, are computed as

$\widetilde{p_1} = 2ucos(w) - \frac{b}{3a}$ and $\widetilde{p_2} = \widetilde{p_{1+}}\ \delta$

where

$$w = (\pi + \cos^{-1}(v/u^3))/3$$

$$v = \frac{b^3}{(3a)^3} - \frac{bc}{6a^2} + d/2a$$

$$u = sign(v)\sqrt{\frac{b^2}{(3a)^2} - \frac{c}{3a}}$$

$$a = 1 + \theta$$

$$b = -(1 + \theta + \widehat{p_1} + \theta\widehat{p_2} + \delta(\theta + 2))$$

$$c = \delta^2 + \delta(2\widehat{p_1} + \theta + 1) + \widehat{p_1} + \theta\widehat{p_2}$$

$$d = -\widehat{p_1}\delta(1 + \delta)$$

$$\theta = n_2/n_1$$

This documentation is based on SAS support link provided as Reference 3 of Section 5.

Appendix 2

Geometric Mean Titer (GMT)

The GMT will be calculated using the following formula:

$$\text{GMT} = 2^{\frac{\sum_{i=1}^{n} \log_2(t_i)}{n}}$$

where $t_1, t_2, \ldots, t_n$ are n observed immunogenicity titers.

Geometric Mean Ratio (GMR)

Geometric mean ratios measure the changes in immunogenicity titers within subjects.

The GMR will be calculated using the following formula:

$$\text{GMR} = 2^{\frac{\sum_{i=1}^{n} \log_2(v_{ij}/v_{ik})}{n}} = 2^{\frac{\sum_{i=1}^{n} \log_2(v_{ij}) - \log_2(v_{ik})}{n}}$$

where for n subjects, v_{ij} and v_{ik} are observed immunogenicity titers for subject i at time points j and k, $j \neq k$.

PAREXEL International Electronic Signature Page

This page is the manifestation of the electronic signature(s) used in compliance with PAREXEL International's electronic signature policies and procedures and in compliance with applicable regulations.

UserName: De, Tuli (det)
Title: Senior Principal Biostatistician, GDO
Date: Monday, 29 April 2019, 06:17 AM GMT Standard Time
Meaning: Document contents approved.
==========