SCHARP
Statistical Center for HIV/AIDS Research and Prevention

STATISTICAL ANALYSIS PLAN

A Phase 3 Trial to Evaluate the Safety, Immunogenicity, and Non-Interference with Concomitant Routine Vaccines, of a Meningococcal Serogroup ACYWX Conjugate Vaccine (NmCV-5) in Comparison with MenACWY-TT Conjugate Vaccine in Healthy Malian Infants

DMID Protocol Number: 20-0024

Effective Date: Date of last signature

Version: 1.0

STATISTICAL ANALYSIS PLAN

Protocol Name:	A Phase 3 Trial to Evaluate the Safety, Immunogenicity, and Non-Interference with Concomitant Routine Vaccines, of a Meningococcal Serogroup ACYWX Conjugate Vaccine (NmCV-5) in Comparison with MenACWY-TT Conjugate Vaccine in Healthy Malian Infants
Protocol Number:	DMID Protocol Number: 20-0024
Version:	1.0

Author(s):

Lead Blinded Statistician	
Legal Name	Clara P. Dominguez Islas, PhD
Signature & Date	See eTMF Signature Manifest

Approvals:

Protocol Chair	
Legal Name	Wilbur Chen, MD, MS
Signature & Date	Wilbur H Chen Digitally signed by Wilbur H Chen DN: C=US, OU=Center for Vaccine Development & Global Health, O=University of Maryland School of Medicine, CN=Wilbur H Chen, E=wilbur.chen@som.umaryland.edu Reason: I am approving this document Location: Date: 2023.06.02 15:26:13-04'00' Foxit PDF Editor Version: 12.1.2

DMID Scientific Lead	
Legal Name	Kevin Schully, PhD
Signature & Date	Kevin L. Schully -S Digitally signed by Kevin L. Schully -S Date: 2023.06.02 09:52:36 -04'00'

The effective date of this document is the date of the latest signature.

TABLE OF CONTENTS

1 LIST OF ABBREVIATIONS AND ACRONYMS

Term/Abbreviation	Definition
AE	adverse event
CI	confidence interval
CSR	Clinical Study Report
eCRF	electronic case report form
EPI	Expanded Program on Immunization
DMID	Division of Microbiology and Infectious Diseases
DSMB	Data and Safety Monitoring Board
GM	geometric mean
GMT	geometric mean titer
HEENT	head, eyes, ears, nose, and throat
IgG	immunoglobulin G
IQR	Inter-quartile range
IU/ml	international units per milliliter
MedDRA	medical dictionary for regulatory activities
MenACWY-TT	quadrivalent meningococcal conjugate vaccine, Nimenrix®
mITT	modified intent-to-treat
mIU/ml	milli-international units per milliliter
MOP	Manual of Procedures
MR	Measles-Rubella (Vaccine)
NmCV-5	meningococcal (A, C, Y, W, X) polysaccharide conjugate vaccine
PP	per protocol
rSBA	rabbit complement serum bactericidal antibody
SAE	serious adverse event
SAP	statistical analysis plan
SCHARP	Statistical Center for HIV/AIDS Research and Prevention
SD	standard deviation
SDSU	Statistical and Data Science Unit
SOC	system organ class
TLFs	tables, listings, and figures
WHO	World Health Organization
WHO-PQ	World Health Organization Pre-Qualification
YF	yellow fever (vaccine)

2 INTRODUCTION

2.1 Purpose

The purpose of this Statistical Analysis Plan (SAP) is to define the statistical analyses planned for the DMID 20-0024 study. DMID 20-0024 is a Phase 3 randomized clinical trial that evaluates the safety, immunogenicity, and non-interference with concomitant routine vaccines, of a meningococcal serogroup ACYWX Conjugate Vaccine (NmCV-5) in comparison with MenACWY-TT Conjugate Vaccine in healthy Malian infants.

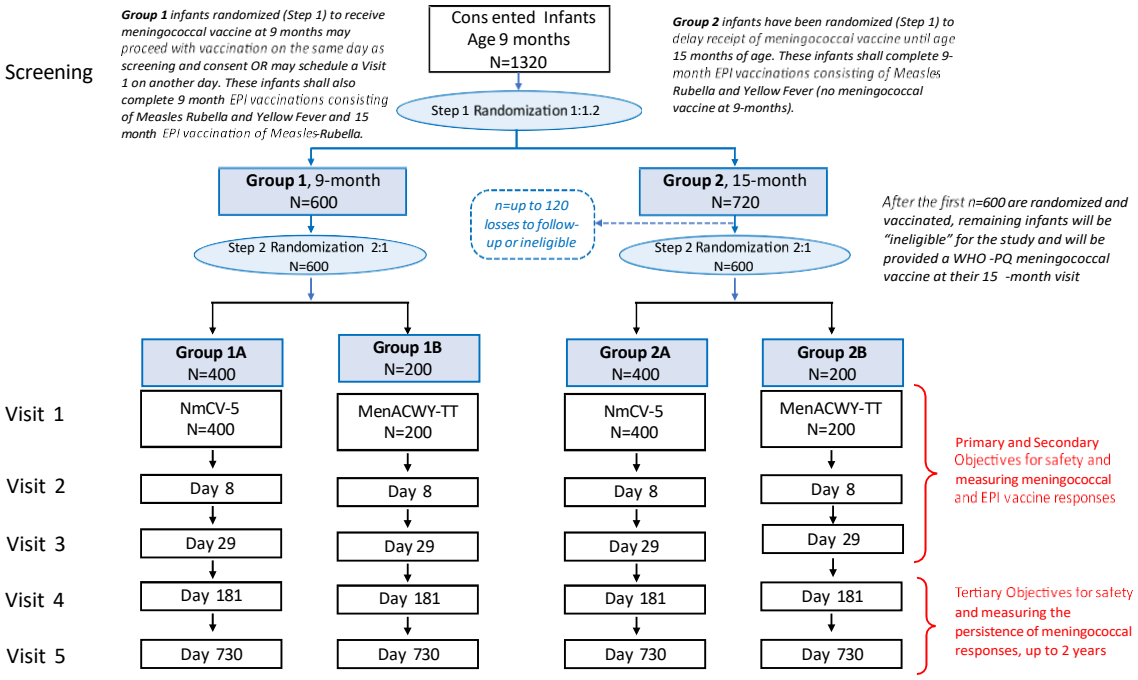
This SAP is based on Version 4.0 of the Study Protocol (23 May 2023) and describes the planned statistical analyses to be conducted for reporting the results of the study. A selected set of the analyses described here may also be included in reports for Data Safety and Monitoring Board (DMSB) reports and be presented in DSMB meetings (see Section 4 of this SAP). A selected set of analyses described here will also be included in reports for WHO in support of the WHO Pre-Qualification (WHO-PQ) application for NmCV-5 (see Section 3.1 of this SAP).

2.2 General Design Considerations

Infants aged 9 months (eligibility 9-11 months) will be consented, enrolled at Step 1, and randomized. A first-step randomization at a 1:1.2 ratio will determine whether the infant will receive blinded meningococcal study product at the 9-month (Group 1, n=600) or the 15-month (Group 2, n=720) enhanced EPI vaccination visit. Within the 9-month or 15-month age groups, a second-step randomization at a 2:1 ratio will determine whether the study participant will receive a single dose of NmCV-5 (Group 1A or 2A) or a single dose of control vaccine, MenACWY-TT (Group 1B or 2B). The infant will be considered enrolled upon the successful first step randomization of the study, which will occur at the time of presenting to their 9-month EPI visit.

If the randomized study product is to be administered at the 15-month visit, the prospectively identified and consented infants will complete their designated “enhanced” EPI immunizations at the 9-month visit, except no meningococcal vaccine will be administered. At their 15-month visit (eligibility 15-17 months), these infants will receive a single dose of NmCV-5 or a single dose of control vaccine, as per the second-step randomization at a 2:1 ratio. Because we anticipate up to 20% of infants may be lost to follow-up (i.e., fail to return to the clinic for their 15-month visit) or may become ineligible (e.g., receives MenAfriVac prior to the 15-month visit), there is the plan to over randomize study infants into the 15-month group—this is the underlying reason for the first-step randomization at 1:1.2. Upon successful randomization of 600 eligible infants into the 15-month groups, all remaining prospectively identified infants (up to n=120) regardless of age upon return will be offered immunization with MenACWY-TT and the “enhanced” EPI vaccinations from available study supply, but otherwise are no longer eligible for the study (i.e., will not be followed in the context of this study)

Figure 1: Schematic of Study Design



In this study, "enhanced" EPI vaccines will be co-administered at indicated time points. There will be a measles and rubella-containing vaccine (i.e., MR) and yellow fever vaccine at 9-months and a second dose of a measles and rubella-containing vaccine at 15-months. Concurrent administration of these EPI vaccines with the blinded study product (i.e., co-administration of these vaccines in the same visit) is acceptable and preferred. Study blood samples are to be obtained at four timepoints for all study infants; at baseline prior to meningococcal vaccination, at 28-days, 6-months and 2 years after meningococcal vaccination. The study is designed to have at least 90% power to meet both the primary non-inferiority objective compared to MenACWY-TT and the objectives related to non-interference with co-administered vaccines.

Table 1: Study Group Design

Group	9 (9) months of age	15[1] (15) months of age	Primary endpoint measurement	Immuno-persistence
1A (n=400)	**NmCV-5** + MR + YF	MR	Serology 28-days post-vaccination	Serology 6-months and 2-years post-vaccination
1B (n=200)	**MenACWY-TT** + MR + YF	MR		
2A (n=400)	MR + YF	**NmCV-5** + MR		
2B (n=200)	MR + YF	**MenACWY-TT** +MR		

NmCV-5 = pentavalent meningococcal conjugate vaccine; MenACWY-TT = quadrivalent meningococcal conjugate vaccine; MR = measles-rubella containing vaccine; YF = yellow fever vaccine.
[1] Once 600 children are randomized to Groups 2A and 2B, the remaining prospectively identified infants (up to n=120) will be provided immunization with MenACWY-TT + MR and will not complete follow up study visits.

The duration of individual subject participation is approximately 24 months (for participants in Groups 1A and 1B) or 30 months (for participants in Groups 2A and 2B), while the estimated time from the beginning of the study to last subject/last study day is approximately 4 years.

2.3 Study Objectives and Endpoints

Table 2: Objectives and Endpoints (Outcome Measures)

Primary Objectives	Primary Endpoints
• To demonstrate that the immune responses to meningococcal serogroups A, C, Y, W, and X elicited by one dose of NmCV-5 at 9 months of age are non-inferior to the immune responses to meningococcal serogroups A, C, Y, W, elicited by one dose of MenACWY-TT at 9 months of age, as measured by rabbit serum bactericidal antibody (rSBA) titers at 28 days after vaccination, and when meningococcal vaccines are given concomitantly with routine vaccines. • To demonstrate that the immune responses to meningococcal serogroups A, C, Y, W, and X elicited by one dose of NmCV-5 at 15 months of age are noninferior to the immune responses to meningococcal serogroups A, C, Y, W elicited by one dose of MenACWY-TT at 15 months of age, measured by rSBA titers at 28 days after vaccination, and when meningococcal vaccines are given concomitantly with routine vaccines.	• The percentage of participants with seroprotective response (rSBA antibody titers ≥ 8) against each meningococcal serogroup A, C, W and Y in the NmCV-5 arm, 28 days after a single dose of meningococcal vaccine, relative to the percentage of participants with seroprotective response against each serogroup A, C, W and Y in the MenACWY-TT arm, among participants vaccinated at either 9 months or 15 months of age. The percentage of participants with seroprotective response to serogroup X in the NmCV-5 arm, to be compared to the percentage of participants with the lowest seroprotective response among serogroups A, C, W and Y in the MenACWY-TT arm.
Secondary Objectives	Secondary Endpoints
• To assess the safety and tolerability of a single dose of NmCV-5 or MenACWY-TT, when given concomitantly with routine vaccines	• All Serious Adverse Events (SAE), reported during the first 6-months of follow-up period after meningococcal vaccination. • All solicited AEs reported during a 7-day follow-up period after meningococcal vaccination. Solicited AEs include injection site tenderness, injection site swelling/induration, injection site erythema, irritability, drowsiness, anorexia, vomiting, fever, and feverishness. • All unsolicited AEs reported through 28 days after meningococcal vaccination
• To demonstrate that the immune responses to meningococcal serogroup X elicited by one dose of NmCV-5 (at either 9 or 15 months of age) is superior to that elicited by MenACWY-TT (at either 9 or 15 months of age) measured by rSBA titers at 28 days after vaccination.	• The percentage of participants with seroprotective response (rSBA antibody titers ≥ 8) to serogroup X in the NmCV-5 arm compared to the percentage of participants with seroprotective response to serogroup X

	MenACWY-TT arm, 28 days after a single dose of meningococcal vaccine
• To demonstrate the non-inferiority of the immune responses to EPI vaccines (measles-rubella, yellow fever, measles booster) when co-administered with NmCV5 (at either 9 or 15 months of age) compared to the immune responses when coadministration with MenACWY-TT (at either 9 or 15 months).	• Proportion of participants with seropositive response for measles and rubella, and seroprotective titers for yellow fever vaccine. The seropositive response to measles vaccine is defined as anti-measles IgG concentration >200 mIU/ml, at Day 29. The seropositive response to rubella vaccine is defined as anti-rubella IgG concentration >20 IU/ml, at Day 29. The seroprotective response to yellow fever vaccine is defined as yellow fever neutralizing antibody titers ≥10.
• To assess clinically significant immune response indicators elicited by a single dose of NmCV-5, given concomitantly with routine vaccines, as compared to those elicited by MenACWY-TT	• Level of rSBA titers (GMTs) against meningococcal serogroups A, C, W, X and Y at 28 days after a single dose of meningococcal vaccine at either 9 or 15 months of age. • • Percentage of participants with seroresponse* in rSBA titers to meningococcal serogroups A, C, W, X and Y at 28 days after a single dose of meningococcal vaccine at either 9 months or 15 months of age (subset of participants). **Seroresponse is defined as a postimmunization (Day 29) rSBA titer of 32 or greater if the participant's pre-immunization (Baseline) rSBA titer was < 8; or a ≥ four-fold increase over baseline at Day 29 postimmunization if the participant's preimmunization rSBA titer was ≥ 8* • Number and proportion of participants with of meningococcal vaccine.
Tertiary Objectives	Tertiary Endpoints
• To assess the safety of a single dose of NmCV-5 or MenACWY-TT through 2 years of follow-up after meningococcal vaccination.	• All SAEs, reported through 2 years of follow-up or during the entire study period.
• To assess the persistence of the immune responses at 6 months and 2 years after meningococcal vaccination.	• The number and proportion of participants with rSBA titers ≥ 8 and ≥ 128 and the calculated rSBA GMTs against each of the five meningococcal serogroups at 6 months and 2 years following meningococcal vaccination
Exploratory Objectives	Exploratory Endpoints

• To compare the immune responses of the 9-month and 15-month group against each of the five meningococcal serogroups at Day 29.	• The comparison of the 9-month and 15- month group proportions of seroprotective response rates and rSBA GMTs against each of the five meningococcal serogroups at Day 29.

2.4 Randomization

Participants will be randomly assigned to one of four possible vaccination schedule arms in two stages. First, enrolled participants will be randomly assigned, in a 1:1.2 ratio, to receive the study vaccine at 9 months of age or at 15 months of age. Participants who are assigned to receive the study vaccine at 9 months of age will be randomly assigned in a 2:1 ratio to receive either NmCV-5 or MenACWY-TT, co-administered with MR and YF EPI vaccines at 9 months of age and followed by a MR vaccine at 15 months of age. Participants who are assigned to receive the study vaccine at 15 months of age will first receive the MR and YF vaccine at 9 months of age. They will later be randomly assigned, in a 2:1 ratio, to receive either NmCV-5 or MenACWYTT, co-administered with the MR vaccine, at 15 months.

To ensure balanced allocation to the four vaccination arms, the randomized assignments will be done in blocks of random sizes, stratified by age group. The randomization scheme will be generated and maintained by SCHARP.

2.5 Blinding

This section describes blinding of researchers and participants to the random assignment of each individual participant (Step 2 randomization) to receive one of two meningitis vaccines (NmCV-5 or MenACWYTT). Random allocation to receive either meningitis vaccine at 9 months of age or at 15 months of age (Step 1 randomization) will be done open label.

Because the study vaccines may have different appearances, it may not be possible for the vaccinator to be blinded. Designated vaccinators will not partake in any post-vaccination evaluation. Parents or guardians of participants, laboratory personnel, and the researchers responsible for evaluation will remain blinded to participants' random assignment of meningitis study vaccine (Step 2 randomization).

The unblinded designated personnel will be provided with the randomization assignment that includes treatment assignment. Based on the assigned treatment the unblinded personnel will prepare the study vaccine to be given to each subject. The unblinded personnel will maintain the randomization assignment in a secure location (apart from the rest of the participant file).

Participants and researchers will remain blinded to individual participant random assignment of meningitis study vaccine until after all scheduled activities related to evaluation and collection of specimens are completed at the last study visit (Visit 5, Study Day 730). Unblinding of individual participants' assignment during the conduct of the trial will be generally avoided, but emergency or non-emergency unblinding may be done for safety reasons, as described in the Study Manual of Procedures (MOP).

2.6 Sample Size and Power

Table 3 shows power to test the non-inferiority of the seroprotective response to each of the serogroups A, C, W and Y elicited by the NmCV-5 vaccine, relative to the seroprotective response elicited by the MenACWY-TT vaccine, when administered as a single dose at either 9 months of age or 15 months of age. These calculations assume a non-inferiority margin of -10% (-0.1) for a one-sided hypothesis test, with a 2.5% Type I error rate, and using the Miettinen-Nurminen method for estimation of the 95% CI for the difference in proportions [1, 2]. The resulting power correspond to the sample size of at least 183 and 366 evaluable participants in each of the MenACWY-TT and NmCV-5 arms, respectively, where this target sample size results from the following assumptions:

- At least 600 enrolled participants will be randomly assigned to receive the study vaccine at 9 months of age and
- Among those randomized to receive the study vaccine at 15 months of age, at least 600 participants will receive it at the scheduled visit.
- For each vaccination age, participants will be randomly assigned, in a 1:2 ratio, to receive the MenACWY-TT or the NmCV-5 vaccine.
- At least 92.5% of the 600 enrolled and vaccinated participants will be followed up and contribute a sample for assessment at their Day 29 visit.

Table 3: Power to test non-inferiority of the proportion of participant with seroprotective response at Day 29 for serogroup A, C, W and Y, for a non-inferiority margin of -10% (-0.1) and a sample size of at least 183 and 366 evaluable participants in MenACWY-TT and NmCV-5 arms, respectively.

Serogroup	Proportion of seroprotective response in MenACWY-TT arm	Difference in proportion of seroprotective response (NmCV-5 – MenACWY-TT)		Power
		Under the Null (H0)	Under the Alternative (H1)	
A	0.95	-0.1	0	99.97%
C	0.95	-0.1	0	99.97%
W	0.90	-0.1	0	97.50%
Y	0.90	-0.1	0	97.50%

Finally, calculation of Power in Table 3 is based on assumed proportions of seroprotective response in the MenACWY-TT arms that are consistent with, if somewhat more conservative than, to those reported in the literature.

Power calculations were performed computationally, based on the exact distribution of the primary endpoint of interest under the alternative hypothesis. The probability of each combination of outcomes in the active and control arms was obtained under the assumption that they follow independent binomial distributions. The power of the test was calculated as the sum of probabilities of those scenarios where the outcomes meet the non-inferiority criterion. A simulation was also conducted to corroborate the results.

Table 4 shows power to test the non-inferiority of the seroprotective response to serogroup X. Unlike serogroups A, C, W and Y, non-inferiority of the vaccine for serogroup X will be based on the difference in the proportion of participants randomized to receive NmCV-5 with seroprotective response to serogroup X minus the proportion of participants randomized to receive MenACWY-TT with seroprotective response to the serogroup with the lowest proportion of seroprotective response. Thus, for this test, and consistent with our assumptions listed above, we assume that the lowest proportion of seroprotective response in the MenACWY-TT will be 90% or higher.

Table 4. Power to test non-inferiority of the proportion of participant with seroprotective response at Day 29 for serogroup X, when compared to lowest seroprotective response rate among A, C, W, Y serogroups, with a non-inferiority margin of -10% (-0.1) and a sample size of at least 183 and 366 evaluable participants in MenACWY-TT and NmCV-5 arms, respectively.

Serogroup	Lowest Proportion of seroprotective response among Serogroups A, C, W, Y in MenACWY-TT arm	Difference in seroprotective response (Serogroup X in NmCV-5 - lowest proportion among Serogroups A, C, W, Y in MenACWY-TT)		Power
		Under the Null (H0)	Under the Alternative (H1)	
X	0.90	-0.1	0	97.50%

Under the assumption that the test statistics used for the five non-inferiority tests described above are independent, the power to declare overall non-inferiority of NmCV-5 relative to MenACWY-TT at a given vaccination age is calculated to be at least 92.6%. We note, however, that this is a conservative assumption and, given the likely correlation between seroprotective response rates among all the serogroups, the overall power may be higher.

3 GENERAL DATA ANALYSIS CONSIDERATIONS

3.1 Timing of analyses and reporting

The main statistical analyses of the primary and secondary immunogenicity endpoints (up to Day 29 visit) and of secondary safety endpoints (up to 6 months of follow-up) will be completed before the end of the study, as soon as the relevant data is available for each of the age groups. Results from these statistical analyses will be summarized in two reports (one per age group), which may be shared with WHO as part of the PQ process.

A first report to be submitted to WHO will include the analysis of primary and secondary endpoints for participants assigned to receive the study vaccine at 9 months of age (Group 1). This report will be produced after the relevant data from all participants in Group 1 through Visit 4 (Study Day 181) has been entered into the study database and appropriate data quality processes have been completed.

A second report to be submitted to WHO will include the analysis of primary and secondary endpoints for all participants assigned to receive the study vaccine at 15 months of age (Group 2), This report will be produced after the relevant data from all participants in Group 2 through Visit 4 (Study Day 181) has been entered into the study database and appropriate processes to ensure data quality have been completed.

The reports described above (which will be referred to as “WHO Reports”) will provide group level results without blinding or masking of the vaccine arms. The analyses will be conducted by the designated unblinded statistician, after the appropriate processes to ensure data quality are completed. The reports can be made available to a limited number of study team members for review, prior to submission to WHO. The list of study members with access to each report should be pre-approved by DMID and IDCRC representatives.

Version 1.0 of this Statistical Analysis Plan (SAP) will be finalized prior to the analyses for the WHO reports being conducted. Any changes or additions to analyses specified here will be properly documented and reported as "post-hoc" when reported.

A final study report will be completed when all primary and secondary safety, clinical, and immunological endpoint data, cumulated up to the end of the study, are available. Depending on the availability, analysis of tertiary and exploratory endpoints may be reported in the final study report, as an addendum to the final study report, in separate reports or in journal manuscript(s).

Additional reports describing immunogenicity endpoints at Day 181 (part of tertiary objectives), either for Group 1 only or for both Group 1 and Group 2, may be produced prior to the final study report, subject to approval from IDCRC and DMID.

For reporting of endpoints relevant to DSMB reviews, see Section 4.1.

3.2 Analysis Sets

Unless otherwise specified, each of the following definitions refers to two analysis sets: one for Group 1 (participants randomized in Step 1 to receive the study meningococcal vaccine at 9-11 months of age) and one for Group 2 (participants randomized in Step 1 to receive the study meningococcal vaccine at 15-17 months of age).

In cases where an analysis set has also been defined in Section 9 of the Protocol, the definition provided here will supersede that of the protocol.

3.2.1 Modified Intent-to-Treat (mITT) Analysis Sets

All participants who were randomized at Step 1 and Step 2 and who received a study meningitis vaccine (NmCV-5 or MenACWY-TT). Participants who were randomized at Step 1 and Step 2 but did not receive a study meningitis vaccine will be excluded. The analyses for this analysis set will be conducted according to the age group as assigned in Step 1 randomization (regardless of participants being vaccinated outside of the assigned age range) and according to the vaccine arm as assigned in Step 2 randomization (regardless of the actual meningitis vaccine received). Participant's observations will be included in the analysis according to the study visit in which they were collected, regardless of the visit being conducted out of the visit window.

3.2.2 Per Protocol (PP) Analysis Sets

These sets will include participants who:

- Are not later found to have been ineligible at the time of enrollment.
- Completed Step 1 and Step 2 randomizations.
- Received the study meningitis vaccine at the appropriate age range, as assigned in Step 1 randomization:
    - At least 9 months and no older than 12 months ($9.0 \leq age < 12.0$) for participants randomized to Group 1.
    - At least 15 months and no older than 18 months ($15.0 \leq age < 18.0$) for participants randomized to Group 2.

  Inclusion of participants vaccinated outside the assigned age range may occur only if approved by a protocol deviation review committee.
- Received the study meningitis vaccine that was assigned at Step 2 randomization.
- Received the scheduled EPI concomitant vaccines. For participants in Group 1, this means receiving the Measles-Rubella (MR) and Yellow Fever (YF) vaccine concurrently with the study meningitis vaccine when at least 9 months and no older than 12 months. For participants in Group 2, this means having received a first MR vaccine as scheduled at about 9 months of age (at the time of enrolment and Step 1 randomization) and a second MR vaccine concurrently with the study meningitis vaccine when at least 15 months and no older than 18 months of age.
- Had a blood specimen collected at Visit 3, with the collection date (as reported in the "Specimen Collection – Blood" eCRF) between Study Day 29 and Study Day 43 (29+14). This is a wider window than the one specified in the protocol for Visit 3 (Day 29 + 7 days). The decision to extend this window was to avoid over-exclusion of participants considering that rSBA titers to meningitis serogroups are expected to reach peak levels before Day 29 and to remain relatively stable (or at least not to decrease significantly) for several weeks. Inclusion of participants with specimen collection outside the above specified window may occur only if approved by a protocol deviation review committee.
- Had a successful/valid rSBA value determined (and provided) by the corresponding Laboratory for at least one of the meningitis serogroups tested (A, C, W, Y or X).
- Did not have a reported protocol deviation (in addition to those listed above) that could impact the meningitis immunogenicity endpoints, as determined by a protocol deviation review committee.

3.2.3 Baseline Immunogenicity Analysis Sets

This set will include a subset of participants that will be randomly selected for assessment of baseline rSBA titers, from blood samples collected at Day 1 (pre-vaccination). At the time of the finalization of this SAP, this set is intended to include 150 participants from Group 1 and 150 participants from Group 2 (25% of the 600 targeted to be enrolled in each group). From Group 1, 150 participants have been randomly selected from the pool of randomized participants (received Step 1 and Step 2 randomizations) that received a meningitis vaccine and for whom baseline serum specimens were available. A simple random selection was performed, stratifying by vaccine arm. A similar procedure is intended for Group 2. These sets will be used for analyses of endpoints that involve meningitis immunogenicity at baseline (Day 1 visit, pre-vaccination sampling).

3.2.4 Durability Immunogenicity Analysis Sets

These analysis sets will assess the longer-term durability of meningitis immunogenicity based on rSBA titers from blood samples collected at the Day 181 (±14 days) and Day 730 (±45 days) study visits. At the time of the finalization of this SAP, these sets are intended to include up to 300 participants from each of Group 1 and Group 2 (200 from the NmCV-5 arm and 100 from the MenACWY-TT arm in each group).

These sets will include participants who:

- Are included in both the Baseline Immunogenicity Analysis Set and the Per Protocol Analysis Set and had blood collected at the Day 181 (±14 days) or Day 730 (±45 days) study visits (Part A), or
- Are randomly chosen from those participants in the Per Protocol Analysis Set (not included in Part A) who had blood collected at the Day 181 (±14 days) or Day 730 (±45 days) study visits (Part B, with enough randomly selected participants to complete the sample of 300 participants per study group after determining the participants in Part A).

If future circumstances allow for assaying of all collected samples, the Durability Immunogenicity Analysis Set will include all participants in the Per Protocol Analysis Set with blood samples collected at Study Day 181 (±14 days) or Study Day 730 (±45 days).

3.2.5 Participants not fully randomized

This includes participants who were enrolled, received their Group 1 or 2 assignment in Step 1 randomization but who did not proceed to Step 2 randomization. These may include participants randomized at Step 1 who no longer meet eligibility criteria, who are lost to follow-up or who remained in the study but are not randomized in Step 2 because the study reached the limit of Group 2 participants randomized and vaccinated (600). These participants will be terminated from the study and will not contribute to the evaluation of any of the study endpoints, but some of the information collected on these participants will be reported as part of study procedures.

3.3 Statistical Analysis Issues

3.3.1 Stratification

Unless otherwise noted, separate analyses will be conducted on Group 1 and Group 2. This is, each analysis described in this SAP will be conducted for each of the two groups, and each Table/Figure/Listing described will be produced for each of the two groups.

3.3.2 Non-inferiority hypothesis tests

Endpoint specific one-sided non-inferiority hypothesis tests will be conducted under a 2.5% significance level. Each non-inferiority test will be evaluated by calculating a two-sided 95% confidence interval for the difference in proportions of participants with the specific response and comparing the lower bound of the

CI to a non-inferiority margin (otherwise noted, the margin is -0.1 and will be expressed as -10%). No p-values will be reported.

3.3.3 Composite Hypothesis Tests for Non-inferiority of Meningitis Vaccine Immune response

The co-primary objectives of the study are to demonstrate non-inferiority of the NmCV-5 vaccine to elicit a seroprotective response, compared to the MenACWY-TT vaccine, when administered as a single dose at either 9 months of age or 15 months of age. To achieve these co-primary objectives, the study will test the following composite hypothesis:

- Null hypothesis: the seroprotection elicited by NmCV-5 to at least one of the meningococcal serogroups A, C, W, X or Y is inferior to the response elicited by MenACWY-TT
- Alternative hypothesis: the seroprotection elicited by NmCV-5 to all five meningococcal serogroups after one dose of NmCV-5 are non-inferior to those elicited by one dose of MenACWY-TT.

Overall non-inferiority at a given vaccination age (at 9 months of age and at 15 months of age) will be declared if the criteria for non-inferiority of the vaccine seroprotection, as defined above, is achieved in all five serogroups.

3.3.4 Missing data

Missing data on the primary immunogenicity endpoints of interest is anticipated when conducting analyses on the mITT analysis set, with reasons including, but not limited to, loss of follow-up before Day 29, missed Day 29 visit, blood specimen not collected, or unsuccessful rSBA determination. For these analyses, a "complete case" approach will be used. If the proportion of participants with missing data exceeds 10% of the analysis set, an additional analysis using multiple imputation will be conducted. Specific details on the multiple imputation analyses are described in Section 8.2.3.

3.3.5 Issues in data collection

The following are data collection issues that have been identified during the conduct of the study, and for which some considerations will be done in the statistical analysis:

A) **No severity grade recorded for Erythema and Induration (Reactogenicity – Baseline and Early eCRF, and Reactogenicity – Daily Log eCRF):** Because of a programming error, missing values were allowed and not automatically queried when entered in some fields of the Reactogenicity - Daily Log eCRF. The fields affected were the severity grade for Erythema/redness and the severity grade for Induration/swelling, which in both eCRFs appear after the question "Is vaccine-related erythema or induration visible?". The issue resulted in two different patterns of responses, both consistent with the absence of any of these events, being entered by site personnel, as described below:

	Is vaccine-related erythema or induration visible?	Erythema and redness largest diameter	Induration/swelling largest diameter	Erythema /redness	Induration/ swelling
Pattern A	No	[blank]	[blank]	None	None
Pattern B	No	[blank]	[blank]	[blank]	[blank]

For analysis purposes, response pattern B will be considered equivalent to pattern A. This is, for cases showing response pattern B, the absence of severity grade in the corresponding fields will be assumed to indicate that no event was observed, provided that the response that the response

to the question “Is vaccine-related erythema or induration visible?” is “No” and that no other related information (such as diameter) was entered. For these cases, a value of “None” for the severity field will be inputted, for analysis purposes.

B) **Surface excluded from criteria for evaluation of Erythema and Induration Severity (Reactogenicity – Baseline and Early eCRF, and Reactogenicity – Daily Log eCRF):** Following Protocol Version 4.0, which excludes percent of the affected surface area as one of the criteria for evaluation of Erythema/redness and Swelling/induration (Table 6. Toxicity Grading Scale – Solicited Local Reactions), this variable, although collected for some participants, will not be included in analyses. Severity grades for Erythema/redness and Swelling/induration will be reported as entered in the database by site personnel, noting that effort has been made to detect, query, and reconcile cases where responses to related fields do not show the expected consistency.

C) **Feverishness symptom not collected for all participants:** Following Protocol Version 3.0, the symptom of feverishness was added as a solicited event to be collected in the Reactogenicity – Daily Log eCRF. As this addition occurred when the study was underway, the evaluation of symptom severity was not collected for all participants. Specific summaries of this symptom will report as “missing” those participants for whom it was not collected.

4 INTERIM ANALYSIS AND SAFETY MONITORING COMMITTEE

No interim statistical analyses will be conducted, understanding by this the sequential testing of a statistical hypothesis for which adjustment of type I error probability is required.

4.1 Data and Safety Monitoring Board Reports

Safety oversight will be conducted by a DSMB. The DSMB will review SAEs on a regular basis and on an ad hoc basis during the trial. The DMID Medical Monitor and the Independent Safety Monitor (as deemed necessary) will be responsible for reviewing SAEs in real time. If any of the halting rules listed in Section 7.6 of the protocol are met, cumulative safety data from all enrolled subjects will be summarized for DSMB review.

In addition to any unscheduled DSMB reviews resulting from halting rules being met, the DSMB will review cumulative AE data as follows:

- A safety review will be conducted after all participants randomly assigned to receive the meningococcal vaccine at 9 months of age have completed Day 29 visit.
- A safety review will be conducted after all participants randomly assigned to receive the meningococcal vaccine at 15 months of age have completed Day 29 visit.
- As per DSMB request, a review of the available study data from the 9 months of age group subjects will be conducted prior to initiating dosing of subjects randomized to receive meningococcal vaccine at 15 months of age subjects.

The DSMB will have access to closed study reports with information presented by vaccine arm, without masking. This is due to simple masking not being possible under unbalanced randomization (2:1) and other masking strategies deemed cumbersome.

Procedures for DSMB reviews/meetings are defined in the corresponding DSMB charter.

5 GENERAL ANALYSIS METHODS

The following descriptive statistics will be used to summarize continuous outcomes: number of non-missing values, mean and standard deviation, median, interquartile range, and range (minimum and maximum). Descriptive statistics for categorical endpoints may include number of non-missing values, frequencies, relative frequencies, and percentages.

Additionally, descriptive summaries of immunogenicity data may include Geometric Means (GM), proportion of participants showing levels above a certain pre-defined cutoff or proportion of participants achieving a pre-specified increase from baseline.

For selected binary endpoints, 95% exact binomial Confidence Intervals (CI), calculated using the Clopper-Pearson method, may be presented. For GM, the corresponding 95% CIs will be based on the log-transformed endpoint and calculated based on a t-distribution with degrees of freedom equal to n-1 (where n denotes the number of observations).

To identify the different randomization arms/groups, the following naming conventions will be used in this SAP and for reporting and displaying of the data analyses.

- "Participants assigned to receive vaccine at 9 months of age" or "Group 1" will be used to describe those screened and enrolled participants who at Step 1 randomization are assigned to receive their meningitis vaccine immediately, noting that the eligibility age range is 9 to 11 months of age.
- "Participants assigned to receive vaccine at 15 months of age" or "Group 2" will be used to describe those screened and enrolled participants who at Step 1 randomization are assigned to receive their meningitis vaccine about 6 months after Step 1 randomization, noting that the eligibility age range is 15 to 17 months of age.
- Within the two groups described above, the term "by vaccination arm" or simply "by arm" will refer to the groups resulting from random vaccine assignment performed at Step 2 randomization (NmCV-5 vs MenACWY-TT).

All summaries and statistical analyses will be produced using SAS statistical software, Version 9.4 of the SAS System for Linux, Copyright © 2013 SAS Institute Inc [3] (SAS and all other SAS Institute Inc., product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA). The R statistical software [4] can also be used to produce (or replicate) selected figures.

6 TRIAL PARTICIPANT DISPOSITION

6.1 Study Screening, Enrollment and Randomization

From the total number of prospective participants screened, the following will be reported:

- Total number of prospective participants screened
- Number and percentage of participants according to their Eligibility Status at Step 1 randomization (eligible and enrolled, eligible not enrolled, ineligible, incomplete screening, ineligible bub enrolled).
- Among those participants with eligibility status at Step 1 randomization "Eligible/Not Enrolled" or "Ineligible", the number and percentage of participants according to the reasons for ineligibility or not enrollment.
- The number and percentage of participants for whom Step 1 randomization was performed, according to the randomization method employed (online randomization or envelope randomization).

From the total of participants randomized at Step 2, the following will be reported overall and by Step 1 randomization groups (participants assigned to receive the study vaccine at 9 months of age and participants assigned to receive the study vaccine at 15 months of age):

- Number of participants according to their Step 2 randomization assignment

- Number and percentage of participants according to their Eligibility Status at Step 2
- Among those participants with eligibility status at Step 2 randomization “Eligible/Not Enrolled” or “Ineligible”, the number and percentage of participants according to the reasons for ineligibility or not enrollment.
- The number and percentage for whom Step 2 randomization was performed, according to the randomization method employed (online randomization or envelope randomization).

6.2 Vaccine Administration

6.2.1 Administration of Randomized Study Meningococcal Vaccine

Among participants randomly assigned to one of the two study products (NmCV-5 or MenACWY-TT) at Step 2 randomization, the number and proportion of participants that received the vaccine will be reported, as collected in the Meningococcal Vaccine eCRF. The age at the time of vaccination (months) will be summarized (Mean, SD, Median, IQR and Range) along with the age category at the time of vaccination. Among participants for whom the meningococcal vaccine was missed, the primary reason, as collected in the Missed Study Product Administration – Meningococcal eCRF, will be tabulated as number and percentage of participants.

This information will be presented for participants in Group 1 and Group 2 randomly assigned to a study product, overall and by vaccine arm.

6.2.2 Administration of EPI Measles-Rubella and Yellow Fever Vaccines

Administration of EPI vaccines was intended for all participants enrolled in the study, this is, all those for whom Step 1 randomization was performed. The EPI scheduled vaccines include (i) the measles-rubella (MR) vaccinated administered at 9 months of age, (ii) the measles-rubella (MR) vaccine administered at 15 months of age, and (iii) the yellow fever (YF) vaccine administered at 9 months of age.

Among participants with randomization at Step 1 performed, the number and proportion of participants for whom EPI scheduled vaccines were administered will be reported. Among participants for whom one of the scheduled EPI vaccines was missed, the primary reason, as collected in the Missed Study Product Administration – Measles and Rubella and the Missed Study Product Administration – Yellow Fever eCRFs, will be tabulated as number and percentage of participants.

This information will be presented for participants in Group 1 (overall and by vaccine arm), for participants in Group 2 randomized in Step 2 to study product (overall and by vaccine arm) and for participants in Group 2 not randomized in Step 2 to study product.

6.2.3 Administration of Meningococcal Vaccine for participants not fully randomized

Per the protocol, participants in Group 2 who are not randomized to a study product will be offered a non-randomized meningitis (MenACWY-TT) vaccine, intended to be administered at 15 months of age or later. Among this set of participants, the number and proportion who had the vaccine administered by the study team, the age at the time of vaccination (among those who received it) and reasons for vaccine not being administered by the study team (among those who did not receive it), as collected in the Termination Vaccination Status eCRF, will be reported in the final study report.

6.3 Study Termination

Among participants enrolled (those who completed at least Step 1 randomization), the reasons for study termination will be tabulated, with number and percent of participants This information will be presented for participants in Group 1 (overall and by vaccine arm), for participants in Group 2 randomized in Step 2 to study product (overall and by vaccine arm) and for participants in Group 2 not randomized in Step 2 to study product.

6.4 Retention (Visit Completion)

The number and proportion of participants expected to complete and who completed each visit (regardless of whether the visit was completed within the allowable visit window) will be tabulated, by study arm. The number and proportion of completed visits that were completed inside the pre-specified visit window and outside the visit window will also be tabulated, by study arm.

6.5 Serum Specimen Collection for Primary Endpoint Determination

The following information, as collected in the "Specimen Collection – Blood" eCRF will be summarized:

- Number and percentage of participants for whom blood specimen was collected. Among participants for whom a specimen was not collected, the reported reasons will be grouped in categories and the number and percentage of participants in each category will be reported.
- The specimen collection method, with the number and percentage of participants for whom the collection was done by venipuncture or heel stick.
- Number and percentage of participants for whom the minimum required volume was obtained. Among participants for whom the minimum required volume was not obtained, the reported reasons will be grouped in categories and the number and percentage of participants in each category will be reported.
- Number and percentage of participants for whom the sample was stored for shipment to the central lab. Among participants for whom the sample was not stored for shipment, the reported reasons will be grouped in categories and the number and percentage of participants in each category will be reported.

6.6 Protocol Deviations

Protocol deviations, as collected in the Protocol Deviations eCRF, will be reported. The number and type of protocol deviations will be tabulated by vaccine arm. A listing with all the recorded protocol deviations will be presented, including the type of protocol deviation, the description of the deviation, the plans and/or actions taken to address the deviation and the plans or/actions taken to prevent future occurrences.

7 BASELINE DATA

For Group 1 and Group 2, baseline characteristics of participants will be described by vaccination arm. For participants in Group 1, the baseline data described in this section was collected at the Screening Visit only. For participants in Group 2, some of the baseline data described here was collected at the Screening Visit and Visit 1 (occurring from 3 to 6 months after the Screening visit). When data from the two visits is reported, it will be reported and identified as "at time of Screening" or "at time of Vaccination".

7.1 Demographics Characteristics

Summaries of demographic characteristics as collected at baseline, including age at enrollment, sex assigned at birth, ethnicity, and race, will be reported tables by study arm. Summaries for age (months) will include mean and SD, median and number and percentage of participants in age categories (8, 9, 10, 11 months). Summaries for sex, ethnicity and race will include number and percentage of participants reporting each category (noting that for ethnicity and race, participants could report more than one). No statistical tests will be performed.

For DSMB reports, tables of Demographic Characteristics will include all participants fully randomized (Step 1 and Step 2 randomization). For WHO reports tables will be produced for the mITT Analysis Set, the PP Analysis Set and the Baseline Immunogenicity Analysis Set. Reports including durability

immunogenicity endpoints will also include a table for the Durability Immunogenicity Analysis Set. The final study report will also include a table of demographic characteristics for all participants enrolled (completing at least Step 1 randomization), by step 2 randomization (Group 1, Group 2, and not fully randomized).

7.2 Anthropometry and Vital Signs

Summaries of height (cm), weight (kg), body temperature (C), hearth rate (beats/min) and rate of respiration (breaths/min), as collected at baseline, will be presented in a table by vaccine arm. WHO standardized z-scores of length/height-for-age, weight-for-age and weight-for-length/height will be calculated (programmatically) based on participants' age (as calculated from reported date of birth) and reported sex at birth, length/height and weight, and summaries of these z-scores will be also be reported. No statistical tests will be performed.

The length/height-for-weight z-score, as calculated by study site personnel for evaluation of eligibility criteria (z-score > -3.0), will not be reported. However, a thorough review has been conducted to ensure that eligibility based on the site reported z-score was consistent with eligibility based on the calculated z-scores.

For DSMB reports, tables reporting Anthropometry and Vital Signs will include all participants fully randomized (Step 1 and Step 2 randomization). For WHO reports tables will be produced for the mITT Analysis set, the PP Analysis Set and the Baseline Immunogenicity Analysis Set. Reports including durability immunogenicity endpoints will also include a table for the Durability Immunogenicity Analysis Set.

7.3 Meningitis Immune response at Baseline

To evaluate meningitis seroprotective levels at baseline, a descriptive analysis of meningitis rSBA titers at Day 1 (serum specimen collected pre-vaccination) will be conducted. For each of the five serogroups (A, C, W, X, Y), the following descriptive summaries will be tabulated by vaccine arm:

- Geometric Mean Titers (GMT), with 95% confidence intervals.
- Range.
- Number and percentage of participants with rSBA titers ≥ 8.
- Number and percentage of participants with rSBA titers ≥ 128.

These summaries will be provided for the Baseline Immunogenicity Analysis Set.

7.4 Medical History

Conditions and/or events collected in the Medical History eCRF will be coded will be coded by MedDRA for preferred term and corresponding system organ class (SOC). Conditions and/or events collected at baseline will be summarized in tables by vaccine arm. Summaries will include the number and percentage of participants reporting a condition/event by MedDRA/SOC, the number and percentage of participants reporting a gradable condition/event, and among those participants, the maximum severity of the condition/event reported. No statistical tests will be performed.

Reported conditions/events reported as gradable and with severity Grade 1 or higher will be provided in a list, including the description of the medical history condition/event, the severity grade, start date of pre-existing condition/event, if the condition is ongoing (at the time that it was reported) and date that the condition/event ended or was resolved, as collected in the Medical History eCRF.

Tables/listings of Medical History conditions/events at baseline will be produced only for the mITT Analysis Set, and to be included only in reports at the end of the study.

7.5 Physical Exam

Physical exam findings, as collected at baseline in the Physical Exam eCRF, will be summarized in tables by study arm. Summaries will include the number and percentage of participants with findings from each specific Body System reported as: (exam) Not done, Normal, Abnormal. This will be reported for all Body Systems (HEENT, neck, lymph nodes, hearth/cardiovascular, lung/respiratory, liver, spleen, extremities, neurological, skin, other system finding). No statistical tests will be performed.

Findings reported as “Abnormal” will be reported in a listing, including description or other information specified.

Tables/listings of physical exam findings at baseline will be produced only for the mITT Analysis Set, and to be included only in reports at the end of the study.

7.6 Concomitant Medications

Medications collected in the Concomitant Medications eCRF be coded using the most recent version of WHO Drug coding, as per the Safety Management Plan. Concomitant medications reported at baseline will be reported in a listing, including information on indication, start date, date stopped, an indicator of the medication ongoing, the dose units, frequency, and route, and if the medication being taken for a reported AE.

The listing of concomitant medication at baseline will be produced only for the mITT Analysis Set, and to be included only in reports at the end of the study.

8 EVALUATION OF IMMUNOGENICITY ENDPOINTS

8.1 Considerations for reporting of laboratory assay endpoints

As per the Central Assay Plan (CAP), rSBA titers are calculated by the responsible laboratory as the reciprocal of the serum dilution yielding ≥ 50% killing compared to the number of viable bacterial cells. The lower limit of quantification (LLOQ) for rSBA assay is 4. Samples with rSBA titers below 4 will be reported by the laboratory as “<4”. In these cases, a value equivalent to half the LLOQ will be imputed for analysis and reporting purposes. Invalid assay results for individual specimen-serogroup assays may also be reported and labeled by the laboratory (labels may include “insufficient”, “contaminated”, “no titer obtained” or “hemolyzed”). For analysis purposes, these observations will be considered as missing.

Similar considerations will be made for the Measles and Rubella IgG ELISA assay and the Yellow Fever Neutralizing Antibody assay. Information on the specific limits of detection/quantification and identification of invalid results will be obtained from CAP and the respective data transfer plans (DTPs).

8.2 Primary Immunogenicity Analyses

Objectives:

- To demonstrate that the immune responses to meningococcal serogroups A, C, W, Y and X elicited by one dose of NmCV-5 at 9 months of age are non-inferior to the immune responses to meningococcal serogroups A, C, W and Y, elicited by one dose of MenACWY-TT at 9 months of age, as measured by rabbit serum bactericidal antibody (rSBA) titers at 28 days after vaccination, and when meningococcal vaccines are given concomitantly with routine vaccines.
- To demonstrate that the immune responses to meningococcal serogroups A, C, W, Y and X elicited by one dose of NmCV-5 at 15 months of age are noninferior to the immune responses to meningococcal serogroups A, C, W and Y elicited by one dose of MenACWY-TT at 15 months of age, measured by

rSBA titers at 28 days after vaccination, and when meningococcal vaccines are given concomitantly with routine vaccines.

For each of the group randomized to receive the meningitis vaccine at 9 months of age or 15 months of age, there are two sets of hypotheses of interest related to the primary objectives that will be assessed as follows.

8.2.1 Non-inferiority of seroprotection for meningitis serogroups A, C, W and Y

Hypothesis:	Null hypothesis: The immune response to meningitis serogroup "S" at Day 29 elicited by one dose of NmCV-5 is inferior to the immune response elicited by one dose of MenACWY-TT, Alternative hypothesis: The immune response to meningitis serogroup "S" at Day 29 elicited by one dose of NmCV-5 is non-inferior, by a pre-specified margin, to the immune response elicited by one dose of MenACWY-TT, where "S" denotes one of the meningitis serogroups: A, C, W or Y.
Endpoint:	• Seroprotective response at Study Day 29 to serogroups A, C, W and Y in the NmCV-5 arm, • Seroprotective response at Study Day 29 to serogroups A, C, W and Y in the MenACWY-TT arm, with seroprotective response defined as serogroup specific rSBA antibody titers ≥ 8.
Strata:	Meningitis vaccination age group: Group 1 (9-11 months) and Group 2 (15-17 months of age).
Analysis Set(s):	The primary analysis will be conducted on the Per Protocol (PP) Analysis Set, with a secondary analysis conducted on the mITT Analysis Set.
Approach:	The proportion of infants with a seroprotective response (randomized to NmCV-5 vs. MenACWY-TT) will be calculated for each of the serogroups A, C, W and Y as $$p_{V,S} = \frac{\sum_{i=1}^{N_V} I(Y_i^{V,S} \geq 8)}{N_V} = \frac{n_{V,S}}{N_V},$$ where V indicates arm (NmCV-5 vs. MenACWY-TT), S indicates serogroup, N_V is the number of infants in the analysis set randomized to arm V and $Y_i^{V,S}$ is the rSBA antibody titer to the S^{th} serogropup for the i^{th} infant in arm V. NmCV-5 will be deemed non-inferior to MenACWY-TT for serogroup S if the lower limit of the 95% confidence interval for $p_{NmCV-5,S} - p_{MenACWY-TT,S}$ excludes -0.10. Confidence Intervals will be calculated using the Miettinen-Nurminen method [1, 2].
Reporting:	The number ($n_{V,S}$) and proportion ($p_{V,S}$) of participants with seroprotective response will be provided (by arm), along with point and 95% CI estimates of the difference in proportions ($p_{NmCV-5,S} - p_{MenACWY-TT,S}$). Proportions and difference in proportions will be reported as percentages (number of infants per 100), with one decimal place.
Graphical display:	Point estimates and 95% CIs for $p_{NmCV-5,S} - p_{MenACWY-TT,S}$ will be displayed graphically in a forest plot, with the non-inferiority margin (expressed as -10%) included as reference.

8.2.2 Non-inferiority of seroprotection to meningitis serogroup X

Hypothesis:	Null hypothesis: The immune response to meningitis serogroup X at Day 29 elicited by one dose of NmCV-5 is inferior to the lowest immune response at Day 29 (among meningitis serogroups A, C, W or Y) elicited by one dose of MenACWY-TT. Alternative hypothesis: The immune response to meningitis serogroup X at Day 29 elicited by one dose of NmCV-5 is non-inferior, by a pre-specified margin, to the lowest immune response at Day 29 (among meningitis serogroups A, C, W or Y) elicited by one dose of MenACWY-TT.
Endpoints:	• Seroprotective response at Study Day 29 to serogroup X in the NmCV-5 arm, • The minimum of the seroprotective responses at Study Day 29 among serogroups A, C, W and Y in the MenACWY-TT arm, with seroprotective response defined as serogroup specific rSBA antibody titers ≥ 8.
Strata:	Meningitis vaccination age group: Group 1 (9-12 months) and Group 2 (15-18 months of age).
Analysis Set(s):	The primary analysis will be conducted on the Per Protocol (PP) Analysis Set, with a secondary analysis conducted on the mITT Analysis Set.
Approach:	The proportion of infants in the NmCV-5 arm with seroprotective response to serogroup X ($p_{\mathrm{NmCV-5},X}$) will be compared to the proportion of infants MenACWY-TT arm with the lowest seroprotective response among serogroups A, C, W and Y ($p_{\mathrm{MenACWY-TT},S}\ for\ S \in (A,C,W,Y)$). NmCV-5 serogroup X protection will be deemed non-inferior to the lowest of the MenACWY-TT serogroups A, C, W, Y protection if the lower limit of the 95% confidence interval for $p_{\mathrm{NmCV-5},X} - \min_{S\in(A,C,W,Y)} p_{\mathrm{MenACWY-TT},S}$ excludes -0.10. Given the additional uncertainty introduced by identifying of the serogroup with the minimum seroprotective response and the estimation of that minimum proportion, confidence intervals for $p_{\mathrm{NmCV-5},X} - \min_{S\in(A,C,W,Y)} p_{\mathrm{MenACWY-TT},S}$ will be estimated using the bootstrap technique. Bootstrap resampling will be performed stratifying by vaccine arm and the 95% CI will be estimated as the interval between the 2.5th and 97.5th percentiles of the bootstrap empirical distribution.
Reporting:	The number ($n_{\mathrm{NmCV-5,X}}$) and proportion ($\mathrm{p}_{\mathrm{NmCV-5,X}}$) of participants with seroprotective response to serogroup X in the NmCV-5 arm, along with point and 95% CI estimates for $p_{\mathrm{NmCV-5},X} - \min_{S\in(A,C,W,Y)} p_{\mathrm{MenACWY-TT},S}$. Proportions and difference in proportions will be reported as percentages (number of infants per 100), with one decimal place.
Graphical display:	The point estimate and 95% CI for $p_{\mathrm{NmCV-5},X} - \min_{S\in(A,C,W,Y)} p_{\mathrm{MenACWY-TT},S}$ will be displayed graphically in a forest plot, with the non-inferiority margin (expressed as -10%) included as reference.

8.2.3 Imputation Analyses for primary endpoints on mITT analysis set

If more than 10% of participants in the mITT analysis have one or more of the meningitis serogroup endpoints missing, an imputation analysis will be conducted in addition to a complete case analysis. Separate imputation analyses will be done for Group 1 and in Group 2.

Step 1 - Model specification:
As a first step, a model to predict seroprotective response to meningitis serogroups will be constructed. Rather than modeling the seroprotective response as a binary endpoint, continuous log10 rSBA levels will be modeled, from which seroprotective response will be derived as defined for primary endpoints. Five separate linear regression models will be fitted on participants with complete response pattern (non-missing seroprotective response to all serogroups), with each of the rSBA log-10 titers to serogroups A, C, W, Y and X as the outcomes of interest. Each model will include a minimum set of predictors (vaccine arm, sex at birth, age at time of vaccination), with additional candidate variables being evaluated for inclusion. A backward stepwise regression analysis will be used to identify which of the additional candidate variables are associated to each of the rSBA. A single model will be used in the imputation step, with final set of predictors including the minimum set specified above and any additional candidate variable associated to any of the serogroups, as given by a p-value of at least 0.1 in at least one of the regression models.

The list of additional candidate variables to be evaluated for inclusion are shown below. Among binary variables, only those showing at least 5 participants in each category will be considered for inclusion, and among categorical variables, only those categories with at least 10 participants will be specified.

- Additional demographic baseline characteristics, as collected at enrollment (race, ethnicity)
- Vital signs, at time of vaccination (body temperature, heart rate, rate of respiration)
- Indicator for availability of baseline rSBA level, for all serogroups
- Indicator of rSBA titers above detectable levels, for all serogroups (only for those with available baseline rSBA levels)
- The log10 rSBA titer for all serogroups (only for those with detectable baseline rSBA levels)
- Indicators for at least one event reported in the Medical History, grouped by MedDRA coded SOC

Step 2 – Imputation:
Imputation of rSBA levels will be conducted using MI Procedure in SAS. Depending on the type of missing pattern, either a monotone regression method (for a monotone pattern of missingness) or fully conditional (FCS) method (for an arbitrary pattern of missingness) will be used. All variables identified in the model specification step will be included. A total of 25 complete datasets with imputed outcomes will be produced.

Step 3 - Analysis and combining results:
After imputation, complete imputed datasets will be analyzed, as specified in Section 8.2.1 and 8.2.2, to obtain the relevant test statistics. The MIANALIZE Procedure in SAS will be used to obtain point and interval estimates of relevant test statistics, which incorporate within-imputation and between-imputation variance. Results will be presented as described for the results of the main analysis.

8.3 Secondary Immunogenicity Analyses

Objectives:

- To demonstrate that the immune responses to meningococcal serogroup X elicited by one dose of NmCV-5 (at either 9 or 15 months of age) is superior to that elicited by MenACWY-TT (at either 9 or 15 months of age) measured by rSBA titers at 28 days after vaccination.
- To demonstrate the non-inferiority of the immune responses to EPI vaccines (measles-rubella, yellow fever, measles booster) when co-administered with NmCV5 (at either 9 or 15 months of

age) compared to the immune responses when co-administered with MenACWY-TT (at either 9 or 15 months).
- To assess clinically significant immune response indicators elicited by a single dose of NmCV-5, given concomitantly with routine vaccines, as compared to those elicited by MenACWY-TT.

8.3.1 Superiority immune responses to meningococcal serogroup X

Hypothesis:	Null hypothesis: The immune response to meningitis serogroup X at Day 29 elicited by one dose of NmCV-5 is not superior to the immune response elicited by one dose of MenACWY-TT, Alternative hypothesis: The immune response to meningitis serogroup X at Day 29 elicited by one dose of NmCV-5 is superior, by a pre-specified margin, to the immune response elicited by one dose of MenACWY-TT.
Endpoints:	• Seroprotective response to serogroup X in the NmCV-5 arm at Day 29, • seroprotective response to serogroup X MenACWY-TT arm at Day 29, with seroprotective response is defined as rSBA antibody titers ≥ 8.
Strata:	Age group (from Step 2 randomization): Group 1 (9-12 months) and Group 2 (15-18 months of age).
Analysis Set(s):	The primary analysis will be conducted on the Per Protocol (PP) Analysis Set, with a secondary analysis conducted on the Meningitis mITT Analysis Set.
Approach:	The proportion of infants (randomized to NmCV-5 vs. MenACWY-TT) with a seroprotective response to serogroup X will be calculated as $$p_{V,X} = \frac{\sum_{i=1}^{N_V} I(Y_i^{V,X} \geq 8)}{N_V} = \frac{n_{V,X}}{N_V},$$ where V indicates arm (NmCV-5 vs. MenACWY-TT), X indicates serogroup X, N_V is the number of infants in the analysis set randomized to arm V and $Y_i^{V,X}$ is the rSBA antibody titer to serogroup X for the i^{th} infant in arm V. NmCV-5 will be deemed superior to MenACWY-TT for eliciting a seroprotective response to serogroup X, by at least 30%, if the lower limit of the 95% confidence interval for $p_{NmCV-5,X} - p_{MenACWY-TT,X}$ excludes 0.30. Confidence Intervals will be calculated using the Miettinen-Nurminen method [1, 2].
Reporting:	The number ($n_{V,X}$) and proportion ($p_{V,X}$) of participants with seroprotective response will be provided (by arm), along with point and 95% CI estimates of the difference in proportions ($p_{NmCV-5,X} - p_{MenACWY-TT,X}$).
Graphical display:	None

8.3.2 Non-inferiority of the seropositive response to Measles vaccine

Hypothesis:	Null hypothesis: The immune response to measles at Day 29 elicited by the MR vaccine when co-administered with one dose of NmCV-5 is inferior to the immune response elicited by the MR vaccine when co-administered with one dose of MenACWY-TT,

	Alternative hypothesis: The immune response to measles at Day 29 elicited by the MR vaccine when co-administered with one dose of NmCV-5 is non inferior, by a pre-specified margin, to the immune response elicited by the MR vaccine when co-administered with one dose of MenACWY-TT.
Endpoints:	Seropositive response to measles vaccine at Day 29 post vaccination, defined as anti-measles IgG concentration >200 mIU/ml.
Strata:	Meningitis vaccination age group: Group 1 (9-12 months) and Group 2 (15-18 months of age).
Analysis Set(s):	Per Protocol (PP) Analysis Set.
Approach:	The proportion of infants with a seropositive response to measles vaccine at Day 29 will be calculated as: $$p_V^{Measles} = \frac{\sum_{i=1}^{N_V} I(M_i^V > 200)}{N_V} = \frac{n_V^{Measles}}{N_V},$$ where V indicates arm (NmCV-5 vs. MenACWY-TT), N_V is the number of infants in the analysis set randomized to arm V and M_i^V is the anti-measles IgG concentration (in mIU/ml) at Day 29 for i^{th} infant in arm V. The NmCV-5 co-administered MR vaccine will be deemed non-inferior to the MenACWY-TT co-administered MR vaccine in eliciting seropositive response to measles if the lower limit of the 95% confidence interval for $p_{NmCV-5}^{Measles} - p_{MenACWY-TT}^{Measles}$ excludes -0.10. Confidence Intervals will be calculated using the Miettinen-Nurminen method [1, 2].
Reporting:	The number ($n_V^{Measles}$) and proportion ($p_V^{Measles}$) of participants with seropositive response to measles will be provided (by arm), along with point and 95% CI estimates of the difference in proportions ($p_{NmCV-5}^{Measles} - p_{MenACWY-TT}^{Measles}$). Proportions and difference in proportions will be reported as percentages (number of infants per 100), with one decimal place.
Graphical display:	Point estimates and 95% CIs for $p_{NmCV-5}^{Measles} - p_{MenACWY-TT}^{Measles}$ will be displayed graphically in a forest plot, with the non-inferiority margin (expressed as -10%) included as reference.

8.3.3 Non-inferiority of the seropositive response to Rubella vaccine

Hypothesis:	Null hypothesis: The immune response to rubella at Day 29 elicited by the MR vaccine when co-administered with one dose of NmCV-5 is inferior to the immune response elicited by the MR vaccine when co-administered with one dose of MenACWY-TT, Alternative hypothesis: The immune response to rubella at Day 29 elicited by the MR vaccine when co-administered with one dose of NmCV-5 is non inferior, by a pre-specified margin, to the immune response elicited by the MR vaccine when co-administered with one dose of MenACWY-TT,
Endpoints:	Seropositive response to rubella vaccine at Day 29 post vaccination, defined as anti-rubella IgG concentration > 20 IU/ml.
Strata:	Meningitis vaccination age group: Group 1 (9-12 months) and Group 2 (15-18 months of age).

Analysis Set(s):	Per Protocol (PP) Analysis Set.
Approach:	The proportion of infants with a seropositive response to measles vaccine at Day 29 will be calculated as: $$\mathrm{p}_V^{Rubella} = \frac{\sum_{\mathrm{i}=1}^{\mathrm{N_V}} \mathrm{I}(R_{\mathrm{i}}^{\mathrm{V}} > 20)}{\mathrm{N_V}} = \frac{n_V^{Rubella}}{\mathrm{N_V}},$$ where V indicates arm (NmCV-5 vs. MenACWY-TT), $\mathrm{N_V}$ is the number of infants in the analysis set randomized to arm V and $\mathrm{R_i^V}$ is the anti-rubella IgG concentration (in IU/ml) at Day 29 for i[th] infant in arm V. The NmCV-5 co-administered MR vaccine will be deemed non-inferior to the MenACWY-TT co-administered MR vaccine in eliciting seropositive response to rubella if the lower limit of the 95% confidence interval for $\mathrm{p}_{NmCV-5}^{Rubella} - \mathrm{p}_{MenACWY-TT}^{Rubella}$ excludes -0.10. Confidence Intervals will be calculated using the Miettinen-Nurminen method [1, 2].
Reporting:	The number ($n_V^{Rubella}$) and proportion ($\mathrm{p}_V^{Rubella}$) of participants with seropositive response to rubella will be provided (by arm), along with point and 95% CI estimates of the difference in proportions ($\mathrm{p}_{NmCV-5}^{Rubella} - \mathrm{p}_{MenACWY-TT}^{Rubella}$).
Graphical display:	Point estimates and 95% CIs for $\mathrm{p}_{NmCV-5}^{Rubella} - \mathrm{p}_{MenACWY-TT}^{Rubella}$ will be displayed graphically in a forest plot, with the non-inferiority margin (expressed as -10%) included as reference.

8.3.4 Non inferiority of the seroprotective response to yellow fever vaccine

Hypothesis:	Null hypothesis: The immune response to yellow fever at Day 29 elicited by the yellow fever vaccine when co-administered with one dose of NmCV-5 is inferior to the immune response elicited by the yellow fever vaccine when co-administered with one dose of MenACWY-TT. Alternative hypothesis: The immune response to yellow fever at Day 29 elicited by the yellow fever vaccine when co-administered with one dose of NmCV-5 is non inferior, by a pre-specified margin, to the immune response elicited by the yellow fever vaccine when co-administered with one dose of MenACWY-TT.
Endpoints:	Seroprotective response to yellow fever vaccine at Day 29 post vaccination, defined as yellow fever neutralizing antibody titers ≥10.
Strata:	Not applicable for this endpoint.
Analysis Set(s):	Per Protocol (PP) Analysis Set (defined in Group 1 only).
Approach:	The proportion of infants with a seroprotective response to yellow fever vaccine at Day 29 will be calculated as: $$\mathrm{p}_V^{YF} = \frac{\sum_{\mathrm{i}=1}^{\mathrm{N_V}} \mathrm{I}(F_{\mathrm{i}}^{\mathrm{V}} \geq 10)}{\mathrm{N_V}} = \frac{n_V^{YF}}{\mathrm{N_V}},$$ where V indicates arm (NmCV-5 vs. MenACWY-TT), $\mathrm{N_V}$ is the number of infants in the analysis set randomized to arm V and $F_{\mathrm{i}}^{\mathrm{V}}$ is the yellow fever neutralizing antibody titers at Day 29 for i[th] infant in arm V. The NmCV-5 co-administered YF vaccine will be deemed non-inferior to the MenACWY-TT co-administered YF vaccine in eliciting seroprotective response to

	yellow fever if the lower limit of the 95% confidence interval for $p_{NmCV-5}^{YF} - p_{MenACWY-TT}^{YF}$ excludes -0.10. Confidence Intervals will be calculated using the Miettinen-Nurminen method [1, 2].
Reporting:	The number (n_V^{YF}) and proportion (p_V) of participants with seroprotective response will be provided (by arm), along with point and 95% CI estimates of the difference in proportions ($p_{NmCV-5}^{YF} - p_{MenACWY-TT}^{YF}$).
Graphical display:	Point estimates and 95% CIs for $p_{NmCV-5}^{YF} - p_{MenACWY-TT}^{YF}$ will be displayed graphically in a forest plot, with the non-inferiority margin (expressed as -10%) included as reference.

8.3.5 Level of rSBA titers and seroresponse at Day 29

A descriptive analysis of the distribution of rSBA titers at Day 29 will be conducted, as follows:

Endpoint:	rSBA titers against meningococcal serogroups A, C, W, X and Y, from samples collected at Visit 3 (Study Day 29).
Analysis Set:	Per Protocol (PP) Analysis Set and the Baseline Immunogenicity Analysis Set
Approach and reporting:	For each of the five serogroups (A, C, W, X, Y), the Geometric Mean Titer (GMT) Ratio of rSBA titers at Day 29 for NmCV-5 relative to MenACWY-TT will be estimated, along with 95% CIs. The point and interval estimates will be obtained from a back transformation of the estimated difference in means of the log-transformed rSBA titers. This analysis will only apply to the Per Protocol Analysis Set. For each of the five serogroups (A, C, W, X, Y), descriptive summaries for rSBA titers at Day 29 will be tabulated by arm. These will include: - Geometric Mean Titers (GMT), with 95% confidence intervals. - Range. - Number and percentage of participants with rSBA titers ≥ 8. - Number and percentage of participants with rSBA titers ≥ 128.
Graphical display:	Reverse Cumulative Distribution plots will be produced to show the distribution of Day 29 rSBA titers, by serogroup and vaccine arm.

For a subset of participants, the following descriptive analysis will be conducted:

Endpoint:	Seroresponse in rSBA titers to meningococcal serogroups A, C, W, X and Y, from samples collected at Visit 3 (Study Day 29), where seroresponse is defined as a post-immunization (Day 29) rSBA titer of 32 or greater if the participant's pre-immunization (Baseline) rSBA titer was < 8; or a ≥ four-fold increase over baseline at Day 29 post-immunization if the participant's pre-immunization rSBA titer was ≥ 8.
Analysis Set:	Baseline Immunogenicity Analysis Set
Approach and reporting:	For each of the five serogroups (A, C, W, X, Y), the number and percentage of participants who show seroresponse in rSBA titers will be reported, by vaccine arm. Additionally, the Geometric Mean Fold Rise (GMFR) from baseline to Day 29 of rSBA titers to meningococcal

serogroups A C, W, X and Y will be estimated, with 95% CI. The point and interval estimates will be obtained from a back transformation of the estimated mean difference of the log-transformed rSBA titers.

8.4 Tertiary Immunogenicity Analysis

Objective:	To assess the persistence of the immune responses at 6 months and 2 years after meningococcal vaccination.
Endpoints:	rSBA titers against meningococcal serogroups A, C, W, X and Y, from samples collected at Visit 4 (Study Day 181, approximately 6 months after meningococcal vaccination) and Visit 5 (Study Day 730, approximately 2 years after meningococcal vaccination).
Analysis Set:	Durability Immunogenicity Analysis Set
Approach and reporting:	For each of the five serogroups (A, C, W, X, Y), descriptive summaries for rSBA titers at Day 181 and Day 730 will be tabulated by vaccine arm. These will include: - Geometric Mean Titers (GMT), with 95% confidence intervals. - Range. - Number and percentage of participants with rSBA titers ≥ 8. - Number and percentage of participants with rSBA titers ≥ 128. - Geometric Mean Fold Rise (GMFR) from baseline, with 95% CI, for those participants in the Baseline Immunogenicity Analysis Set.

8.5 Exploratory Immunogenicity Analysis

Objective:	To compare the immune responses of the 9-month and 15-month group against each of the five meningococcal serogroups at Day 29.
Endpoints:	rSBA titers against meningococcal serogroups A, C, W, X and Y, from samples collected at Visit 3 (Study Day 29). Seroprotective response at Study Day 29 to serogroups A, C, W, Y and X, with seroprotective response defined as serogroup specific rSBA antibody titers ≥ 8.
Analysis Set:	Analyses may include participants in the Per Protocol (PP) Analysis Sets and the mITT Analysis Sets.
Approach:	The association of meningitis immune response 29 days post vaccination and age of meningitis vaccine administration will be explored through linear and/or logistic regression analyses (on the continuous log10 rSBA titers, or the seroprotective response binary endpoints, respectively). This approach will allow estimation of this association averaged across meningitis vaccines and meningitis serogroups, as well as adjustment for participants' characteristics and testing of potential effect modifiers. Being an exploratory objective/endpoint, the need for flexibility in the use of alternative or additional approaches is acknowledged.

8.6 Additional Immunogenicity Analysis

Although not specified in the protocol, additional summaries will be reported, to support assessment of the immune response to EPI scheduled vaccines concomitantly administered with NmCV-5 or MenACWY-TT. The endpoints include the Day 29 anti-measles IgG concentration, the anti-rubella IgG concentration, and the yellow fever neutralizing antibody titers. The analyses will be conducted in the Per Protocol Analysis Set. For each of the endpoints, descriptive summaries, including range and geometric mean titers with 95% confidence intervals, will be tabulated by vaccine arm.

9 SAFETY SECONDARY OBJECTIVES

9.1 Solicited Local and Systemic Adverse Events (Reactogenicity)

(Secondary) Endpoint: All solicited AEs reported during a 7-day follow-up period after meningococcal vaccination.

Per protocol, solicited injection site (local) and systemic reactogenicity adverse events are intended to be collected from time of study meningococcal vaccination through 7 days after each vaccination. Reactogenicity is intended to be first assessed about 30 minutes post-vaccination, then routinely assessed during the first four days post-vaccination and again on Day 8 Visit (Study Visit 2, scheduled at Day 8 with + 3-day window). For instances where there is reactogenicity of grade 2 or higher at the fourth day post-vaccination (Day 5), then daily assessments are intended to continue, until resolution or the severity of the reactogenicity is grade 1 (Mild). Severity grade for solicited AEs is recorded as none, mild, moderate, Severe and Potentially Life Threatening. Systemic AEs include Body temperature, Irritability, Drowsiness/Lethargy, Decrease Eating/Anorexia, Vomiting and Feverishness. Local AEs include erythema/redness (severity and largest diameter in cm), induration/swelling (severity grade and largest diameter in cm), and pain and/or tenderness.

For this safety endpoint, all reactogenicity symptoms reported after receipt of meningitis vaccination at Study Day 1 to Day 7 (including early assessment post-vaccination) will be included, as well as symptoms reported for Study Day 8, as long as the Day 8 assessment visit occurred within the specified visit window. Symptoms will be reported according to the Study Day for which they were reported in the Reactogenicity - Baseline and Early and Reactogenicity - Daily Log eCRFs.

Analysis Set: mITT Analysis Set

Approach: For each systemic and local solicited AE, the maximum severity reported by participants after vaccination, as collected in the Reactogenicity – Daily Log eCRF will be summarized. The number and percentage of subjects reporting each AE will be presented in tables by Symptom, Maximum Severity and vaccine arm. Additionally, the number and percentage of subjects reporting any Systemic Solicited Symptom, any Local Solicited Symptom will be calculated and reported by maximum Severity and vaccine arm. For calculation of percentages, the denominator is the number of subjects in the analysis set (excluding those missing all post-vaccination assessments for the symptom). For local AEs that report largest diameter, summary statistics (mean and SD, median and IQR, range) will be presented.

For each systemic and local solicited AE, bar plots describing the classification (proportion) of participants by the maximum severity of the AE reported, by Study Group, will be produced.

Additional Tables/Listings: All systemic and local solicited AEs will be summarized at the event level, by collection time (Day 1 early assessment and Days 1-8 post-vaccination), Symptom, Severity. For calculation of percentages, the denominator is the number of subjects in the analysis set (excluding those missing assessments for the day and symptom). Summary statistics for largest diameter of local AEs, as appropriate, will also be reported.

9.2 Unsolicited Adverse Events

(Secondary) Endpoint: All unsolicited AEs reported through 28 days after meningococcal vaccination

Unsolicited Adverse Events (AEs) are anticipated to be collected from the time participants received their assigned meningitis vaccination through 28 days after meningitis vaccination. Per the study protocol, the time of reference for the AE is to be the time from receipt of the randomized blinded meningococcal vaccine. Thus, for participants randomized to receive their meningococcal vaccine at 15-18 months, AEs occurring between Step 1 randomization visit and Step 2 randomization visit are not anticipated to be collected and will not be included as part of safety endpoints.

This safety endpoint includes all unsolicited AEs reported in scheduled or interim (unscheduled) visits after receipt of meningitis vaccination and with date of onset up to and including Study Day 29.

Severity grade for unsolicited AEs is evaluated and reported by site investigators as mild, moderate, severe, potentially life-threatening and death. Unsolicited AEs will be coded by MedDRA for preferred term and corresponding system organ class (SOC). Unsolicited AEs will also be classified as related or not related to study product.

Analysis Set: mITT Analysis Set

Approach: The number and percentage of subjects reporting at least one (unsolicited) AE related to study product, overall and for each MedDRA preferred term, will be presented in tables by MedDRA SOC, preferred term, Severity and Study Group. For participants reporting multiple events within the same MedDRA term, the maximum severity grade is counted. Percentages are calculated as the number of participants reporting an event of a specific severity grade divided by the number of participants in the analysis set. Exact 95% CI for the percentage of participants reporting at least one AE, overall and by MedDRA SOC category will be computed.

Graphical display: A bar chart showing unsolicited AEs by MedDRA SOC and severity, as well as a bar chart showing AEs by MedDRA SOC and relationship to study product, will be produced.

Additional Tables/Listings: All Unsolicited AEs will be cross tabulated by severity and relationship to study product, for each Study Group. All adverse events graded as Moderate or above, will be listed. The listing will include Subject ID, MedDRA Preferred Term and AE description verbatim, Severity, Relationship to Study Product, Study Visit where the AE was reported, Onset Date, Time from Vaccination Date to Onset Date, Outcome Date, Duration Days, Action Taken with Study Product, Other Actions, Status/Outcome, if the AE qualifies as SAE, if the AE meet criteria for Suspected Unexpected Serious Adverse reaction (SUSAR), if the event was evaluated for halting criteria and if the AE is a worsening of a baseline medical condition.

9.3 Serious Adverse Events

Secondary Endpoint: All Serious Adverse Events (SAE), reported during the first 6-months of follow-up period after meningococcal vaccination.

Tertiary Endpoint: All SAEs, reported through 2 years of follow-up or during the entire study period, after meningococcal vaccination.

Unsolicited Adverse events that are reported as Serious Adverse Events (SAEs) according to ICH/GCP or Protocol will be collected from the time of Step 2 randomization and vaccination to through study termination, up to 2 years after meningococcal vaccination. For participants randomized to receive their meningococcal vaccine at 15-17 months, SAEs occurring after Step 1 randomization visit but prior to Step 2 randomization visit may be collected but will not be included in the evaluation of vaccine safety endpoints. Their reporting is described in section 9.4.1.

The secondary endpoint includes all SAEs reported in scheduled or interim (unscheduled) visits after receipt of study meningitis vaccine and with date of onset up to and including Study Day 181.

The tertiary endpoint (to be reported only at the end of the study) includes all SAEs collected in scheduled or interim (unscheduled) visits after receipt of study meningitis vaccine and up to and including the last scheduled Study Visit (Visit 5, scheduled for Study Day 730 ± 45 days).

Analysis Set: mITT Analysis Set

Approach: Serious Adverse Events (SAE), as collected in the Adverse Event eCRF, will be reported in listings, by age and meningococcal vaccination arm. The listing will include Subject ID, MedDRA Preferred Term, AE description verbatim, Severity, Relationship to Study Product, Study Visit where the SAE was reported, Onset Date, time to Onset Date (in days) from study meningitis vaccination, Outcome Date, Duration Days, Action Taken with Study Product, Other Actions, Status/Outcome, Criteria that makes the AE and SAE, if the AE meet criteria for Suspected Unexpected Serious Adverse reaction (SUSAR), if the event was evaluated for halting criteria and if the AE is a worsening of a baseline medical condition.

9.4 Other Safety Measures

9.4.1 Serious Adverse Events collected prior to study vaccine administration

For participants randomized to receive their meningococcal vaccine at 15-17 months, SAEs occurring after Step 1 randomization (enrollment visit) but prior to Step 2 randomization visit (and thus prior to receiving meningococcal vaccination) may be collected. These events will not be included in the evaluation of endpoints related to the meningitis vaccine safety, as described in Section 9.3. However, as these events were observed while participants were enrolled in the study, they will be reported. A separate listing for these events (additional to the listings described in Section 9.3) will be produced for the final study report.

9.4.2 Clinical Laboratory Evaluations

No local clinical laboratory data is collected for this study during follow-up.

9.4.3 Malaria Test Results in Follow-up Visits

The total number of malaria rapid tests conducted at follow-up visits only (visits occurring after Visit 1, including interim visits), as collected in the Malaria Test Results eCRF, will be provided in a listing of individual participants. The listing will include study arm and all the information reported in the Malaria Test Results eCRF.

10 REFERENCES

[1] Miettinen, O. and Nurminen, M., 1985. Comparative analysis of two rates. *Statistics in medicine*, *4*(2), pp.213-226.

[2] Newcombe, R.G., 1998. Interval estimation for the difference between independent proportions: comparison of eleven methods. *Statistics in medicine*, *17*(8), pp.873-890.

[3] SAS Institute Inc. 2016. SAS® 9.4 Language Reference: Concepts, Sixth Edition. Cary, NC: SAS Institute Inc.

[4] R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org

11 CHANGE HISTORY

Version		Affected Section(s)	Activity Description
Number	Effective Date		

1.0	Date of last signature		First Version.