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

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Product Sponsor:
SIIPL (Serum Institute of India Pvt. Ltd.)
Pune, India

Protocol Chair: Wilbur Chen, MD, MS

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STATEMENT OF ASSURANCE

Each Institution will hold a current Federal Wide Assurance (FWA) issued by the Office of Human Research Protections (OHRP) for federally funded human subjects research. Each FWA will designate at least one Institutional Review Board (IRB)/Independent Ethics Committee (IEC) registered with OHRP, for which the research will be reviewed and approved by the IRB/IEC and will be subject to continuing review [45 CFR 46.103(b)]. The IRB/IEC designated under an FWA may include an institution's IRB/IEC, an independent IRB/IEC, or an IRB/IEC of another institution after establishing a written agreement with that other institution.

STATEMENT OF COMPLIANCE

The study trial will be carried out in accordance with Good Clinical Practice (GCP) and as required by the following:

- United States Code of Federal Regulations (CFR) 45 CFR Part 46: Protection of Human Subjects
- Food and Drug Administration (FDA) Regulations, as applicable: 21 CFR Part 50 (Protection of Human Subjects), 21 CFR Part 54 (Financial Disclosure by Clinical Investigators), 21 CFR Part 56 (Institutional Review Boards), 21 CFR Part 11, and 21 CFR Part 312 (Investigational New Drug Application), 21 CFR 812 (Investigational Device Exemptions)
- International Conference on Harmonisation: Good Clinical Practice (ICH E6); 62 Federal Register 25691 (1997); and future revisions
- Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- National Institutes of Health (NIH) Office of Extramural Research, Research Involving Human Subjects, as applicable
- National Institute of Allergy and Infectious Diseases (NIAID) Clinical Terms of Award, as applicable
- Applicable Federal, State, and Local Regulations and Guidance

SIGNATURE PAGE

The signature below provides the necessary assurance that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH E6 Good Clinical Practice (GCP) guidelines.

I agree to conduct the study in compliance with GCP and applicable regulatory requirements.

I agree to conduct the study in accordance with the current protocol and will not make changes to the protocol without obtaining the sponsor's approval and IRB/IEC approval, except when necessary, to protect the safety, rights, or welfare of subjects.

Site Investigator Signature:

Signed: _____ Date: _____

Samba Sow, MD
University of Maryland School of Medicine/Center for Vaccine Development – Bamako, Mali

Signed: _____ Date: _____

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
BCG	Bacillus Calmette–Guérin vaccine, for tuberculosis
CDSCO	Central Drugs Standard Control Organisation, DCGI
CFR	Code of Federal Regulations
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CMC	Chemistry, Manufacturing and Control
COI	Conflict of Interest
CRF	Case Report Form
CRM_{197}	Cross reactive material, detoxified mutant diphtheria toxin
CROMS	Clinical Research Operations and Management Support
CSR	Clinical Study Report
CVD	Center for Vaccine Development and Global Heath, Baltimore
CVD-Mali	Centre pour le Développement des Vaccines du Mali
DCC	Data Coordinating Center
DCF	Data Collection Form
DCGI	Drugs Controller General of India
DDE	Direct Data Entry
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases, NIAID
DPM	Departement de Pharmacie et Medicaments
DTwP	Diphtheria, Tetanus, and Pertussis vaccine
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
eCRF	Electronic Case Report Form
ELISA	Enzyme-Linked Immunosorbent Assay
EPI	Expanded Program on Immunization
FDA	Food and Drug Administration
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMT	Geometric Mean Titer
HepB	Hepatitis B virus vaccine
Hib	*Haemophilus influenzae* type b conjugate vaccine
IATA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ID	Identification
IDCRC	Infectious Disease Clinical Research Consortium
IDE	Investigational Device Exemption

IEC	Independent or Institutional Ethics Committee
IM	Intramuscular
IND	Investigational New Drug Application
IPV	Inactivated Polio Vaccine, parenteral
IRB	Institutional Review Board
ISM	Independent Safety Monitor
MAAE	Medically-Attended Adverse Event
MedDRA®	Medical Dictionary for Regulatory Activities
MenA	Monovalent meningococcal serogroup A conjugate vaccine, MenAfriVac®
MenACYW-TT	Quadrivalent meningococcal conjugate vaccine, Nimenrix®
MM	Medical Monitor
MO	Medical Officer
MOP	Manual of Procedures
MR	Measles-Rubella Vaccine
MVP	Meningitis Vaccine Project
N	Number (typically refers to subjects)
NDA	New Drug Application
NIAID	National Institute of Allergy and Infectious Diseases, NIH
NIBSC	National Institute for Biological Standards and Control
NIH	National Institutes of Health, DHHS
NmC	Serogroup C
NmCV-5	Meningococcal (A,C,Y,W,X) polysaccharide conjugate vaccine
NmW	Serogroup W
NmX	Serogroup X
NRA	National Regulatory Agency
OER	Office of Extramural Research
OHRP	Office for Human Research Protections
OPV	Oral Polio Vaccine
PCV	Pneumococcal Conjugate Vaccine
PEI	Paul Ehrlich Institute
PHE	Public Health England
PHI	Protected Health Information
PI	Principal Investigator
PP	Per Protocol
PQ	Pre-Qualification
PS	Polysaccharides
QA	Quality Assurance
QC	Quality Control
rSBA	Rabbit complement serum bactericidal antibody
SA	Secondary Aims
SAE	Serious Adverse Event/Serious Adverse Experience
SAGE	WHO's Strategic Advisory Working Group of Experts
SAP	Statistical Analysis Plan

SCHARP	Statistical Center for HIV/AIDS Research & Prevention, at Fred Hutchinson Cancer Research Center
SDCC	Statistical and Data Coordinating Center
SDSU	Statistical and Data Science Unit
SIIPL	Serum Institute of India Pvt Ltd.
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Event
TT	Tetanus Toxoid
UKHSA	UK Health Security Agency
US	United States
VTEU	Vaccine and Treatment Evaluation Unit
WHO	World Health Organization
YF	Yellow Fever vaccine

PROTOCOL SUMMARY

Title:	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
Design of the Study:	This trial will evaluate a single dose of NmCV-5 administered at either 9 months or 15 months of age, time points in the Expanded Program on Immunization (EPI) schedule when meningococcal vaccine is most likely to be administered. Infants aged 9 months will be consented and randomized to the assigned age group to receive vaccine at 9 months or 15 months. Infants aged 9 months (eligibility 9-11 months) and randomized to the 9-month age group will be randomized in a 2:1 ratio to receive a single dose of NmCV-5 or a single dose of MenACWY-TT. Prospectively identified and consented infants randomized to the 15-month age group will return when aged 15 months (eligibility 15-17 months) and will be randomized in a 2:1 ratio to receive a single dose of NmCV-5 or a single dose of MenACWY-TT. "Enhanced" EPI vaccines will be co-administered and will consist of 2-doses of a measles and rubella-containing vaccine administered at 9 months and 15 months and a single dose of yellow fever vaccine administered at 9 months.
Study Rationale:	Progressive introduction of MenAfriVac since 2010 has resulted in a substantial reduction in cases of serogroup A meningococcal disease. However, regular large-scale epidemics due to serogroups C, W and X remain common in the African meningitis belt. An affordable and scalable pentavalent meningococcal conjugate vaccine (NmCV-5) has been developed by SIIPL, the manufacturer of MenAfriVac. NmCV-5 is designed to protect against serogroups A, C, W, Y and X. The immediate goal for the clinical development of NmCV-5 is for WHO Pre-Qualification (WHO-PQ), to enable the vaccine to be used in the Meningitis Belt of sub-Saharan Africa. The current Phase 3 study, as agreed under the WHO-PQ strategy, is a study of NmCV-5 in the infant Expanded Program on Immunization (EPI) schedule in sub-Saharan Africa. This

	study protocol is designed to provide evidence that concomitant vaccination with NmCV-5 will not significantly affect the immune responses of infants to their normally scheduled EPI vaccines. We have specifically designed this study to provide information at two distinct timepoints, 9 months and 15 months. The WHO-PQ quadrivalent meningococcal conjugate vaccine MenACWY-TT (Nimenrix®, manufactured by Pfizer) is to be the control comparator vaccine to NmCV-5. MenACWY-TT is approved for use in infants as young as 6 weeks of age. WHO supports the evaluation of the age ranges of 9 months and 15 months under which NmCV-5 is intended to be adopted by stakeholder countries in the Meningitis Belt. The current Mali EPI schedule consists of a measles only vaccine, yellow fever vaccine, and MenA vaccine at 9 months of age; there is no 15 months of age EPI vaccine visit and typically only a single dose of a measles-containing vaccine is administered. However, to satisfy the conditions for WHO-PQ, study participants will receive two doses of a measles-containing vaccine, at 9-months and 15-months. Furthermore, the non-inferiority evaluation must include an assessment of the rubella vaccine responses. These modifications to the standard Malian EPI schedule provide a level-of-care that is higher than the current standard-of-care for the general population. Within the context of this study, we will refer to this as an "enhanced" EPI schedule.
Study Phase:	3
Study Population:	Healthy infants aged 9-11 months who reside in Bamako, Mali.
Number of Sites:	1
Description of Study Products:	NmCV-5 (the experimental meningococcal vaccine) is a pentavalent meningococcal (A, C, Y, W, X) polysaccharide-conjugate vaccine composed of capsularpolysaccharides (PS) from *Neisseria meningitidis* serogroups A, C, Y, W, and X individually conjugated to a protein carrier, either mutant diphtheria toxoid (CRM_{197}) or tetanus toxoid (TT).

MenACWY-TT (the comparator meningococcal vaccine) is a WHO-PQ quadrivalent meningococcal (A, C, Y, W) polysaccharide-conjugate vaccine manufactured by Pfizer (known as Nimenrix®).

"Enhanced" EPI Vaccines:
The combined measles-rubella (MR) vaccine is WHO-PQ and manufactured by SIIPL.
The yellow fever (YF) vaccine is WHO-PQ and manufactured by Sanofi Pasteur (Stamaril®).

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 non-inferior 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 in the 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 NmCV-5 (at either 9 or 15 months of age) compared to the immune responses when co-administration 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 ≥ 1:10.*
• 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 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.*

	• Number and proportion of participants with rSBA titers ≥ 128 at 28 days after a single dose of meningococcal vaccine.
Tertiary Objective	Tertiary Endpoint
• 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.

Study Eligibility Criteria:

Inclusion Criteria:

1. Male and female children between 9 months and 11 months old inclusive.
2. Parent(s)/legal guardian(s) have provided written informed consent, after the nature of the study has been explained according to local regulatory requirements.
3. The investigator believes that their parent(s)/guardian(s) will be available for all the subjects visits and will comply with the requirements of the protocol (e.g., timely reporting of adverse events).
4. Individual is in good health as determined by medical history, physical examination, and clinical judgement of the investigator. (*Note: the physical examination may have been performed on a separate screening day and will be considered valid if within 14 days of enrollment*)
5. Individual has completed their local infant EPI vaccines, not including 9-month EPI vaccines (at the 9-month visit) or 15-month EPI vaccines (at the 15-month visit). A birth dose of oral polio vaccine is not required.

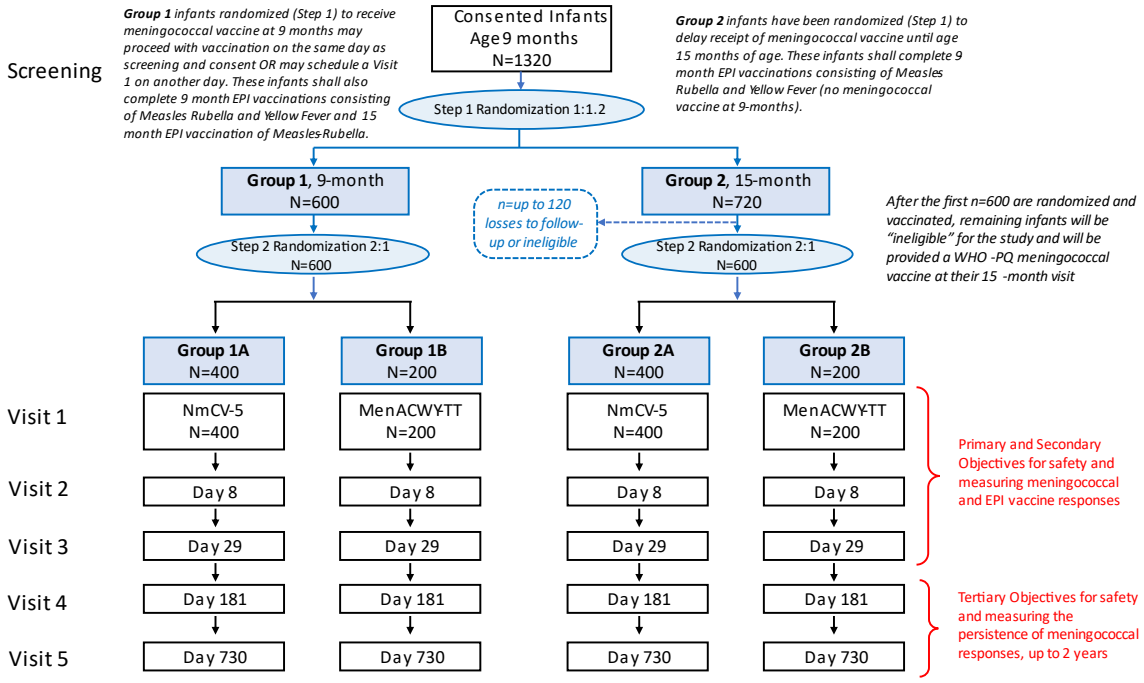
Exclusion Criteria:

1. History of receipt of any meningococcal vaccine.
2. Has received a measles-containing vaccine.
3. Current or previous, confirm or suspected disease caused by *N. meningitidis*.
4. Household contact with and/or intimate exposure to an individual with any laboratory confirmed *N. meningitidis* infection within 60 days of enrolment or study vaccination (for the 15-month age group).
5. History of severe allergic reactions after previous vaccinations or hypersensitivity to any study vaccine component including tetanus, diphtheria and mutant diphtheria toxoid (CRM_{197}).
6. Acute or chronic, clinically significant pulmonary, cardiovascular, metabolic, neurological, hepatic, or renal functional abnormality, as determined by medical history or physical examination.
7. Any confirmed or suspected condition with impaired or altered function of the immune system (e.g., immunodeficiency, autoimmune conditions, malnutrition).
8. Have any bleeding disorder which is considered a contraindication to intramuscular injection or blood draw.
9. Severe acute malnutrition. *Note: a weight-for-length Z-score of less than –3 satisfies this exclusion criteria*.
10. History of either hepatitis B or hepatitis C virus infection, human immunodeficiency virus infection, or hereditary immunodeficiency.
11. Presence of major and clinically significant congenital defects.
12. Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within three months prior to the study vaccination or planned use throughout the study period (for corticosteroids, this means prednisone, or equivalent, ≥ 0.5 mg/kg per day. Inhaled, intranasal, and topical steroids are allowed).
13. Administration of blood, blood products and/or plasma derivatives or any parenteral immunoglobulin preparation in the past 3 months or planned use throughout the study period.

14. Administration of any vaccine within 14 days prior to enrolment in the study or planned administration of any vaccine within 14 days before or after study vaccination.
15. Use of any investigational or non-registered drug or vaccine within 28 days prior to the administration of study vaccine or planned during the study.
16. Malaria infection as confirmed by a Rapid Diagnostic Test. *Note: subjects positive at screening may be treated for malaria as per national guidelines outside of the study, and if the subject remains eligible, vaccinated no earlier than 5 days after completing treatment*.
17. Individuals who are close family member* of individuals conducting this study. **defined as a child with direct genetic relationship to a member of the study team*.
18. Have experienced a moderate or severe acute infection and/or fever (defined as temperature ≥ 37.5°C) within 3 days prior to enrolment or study vaccination.
19. Have received systemic antibiotic treatment within 3 days prior to enrolment or study vaccination.
20. Non-residence in the study area or intent to move out within six months.
21. Any condition which, in the opinion of the investigator, might pose additional risk to the subject due to participation in the study.

Duration of Individual Subject Participation:	Approximately 24 or 30 months
Estimated Time to Last Subject/Last Study Day:	Approximately 4 years

Figure 1: Schematic of Study Design



Schedule of Events

Group 1: Participant Age (9-month group)	9 mon	9 mon	9 mon	10 mon	15 mon	33 mon	
Visit	Screen	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	ET
Study Day		1	8	29	181	730	
Window			+3	+7	±14	±45	
Informed Consent	X						
Demographics[1]	X						
Medical History including review of systems[1]	X						
Determination / Confirmation of Eligibility	X	X					
Rapid Diagnostic Test for malaria		X					
Photo of child		X					
Vital Signs[1,2] including axillary temperature	X		X	X	X	X	(X)
Height, weight[1]	X						
Physical exam[1]	X		X	X	X	X	(X)
Randomization Step 1	X						
Randomization Step 2		X					
Blinded Vaccination		X					
Administration of enhanced EPI vaccines[†]		X			X		
30-minute observation period post meningitis vaccination		X					
7-day Memory Aid (**d**ispense & **c**ollect) [4]		D	C				

AE assessment		X	X	X			(X)
Concomitant medications and vaccinations[1,3]	X	X	X	X			X
SAE assessment		X	X	X	X	X	X
Research Blood Draw (mL)		5 mL		10 mL	5 mL	5 mL	5 mL

Group 2: Participant Age (15-month group)	**9 mon**	**15 mon**	**15 mon**	**16 mon**	**21 mon**	**39 mon**	
Visit	**Screen**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**ET**
Study Day		1	8	29	181	730	
Window			+3	+7	±14	±45	
Informed Consent	X						
Demographics[1]	X						
Medical History including review of systems[1]	X	X					
Determination / Confirmation of Eligibility	X	X					
Rapid Diagnostic Test for malaria		X					
Photo of child		X					
Vital Signs[1,2] including axillary temperature	X	X	X	X	X	X	(X)
Height, weight[1]	X	X					
Physical exam[1]	X	X	X	X	X	X	(X)
Randomization Step 1	X						
Randomization Step 2		X					
Blinded Vaccination		X					
Administration of enhanced EPI vaccines[†]	X	X					
30-minute observation period post meningitis vaccination		X					
7-day Memory Aid (**d**ispense & **c**ollect) [4]		D	C				
AE assessment		X	X	X			(X)
Concomitant medications and vaccinations[1,3]	X	X	X	X			X
SAE assessment		X	X	X	X	X	X
Research Blood Draw (mL)		5 mL		10 mL	5 mL	5 mL	5 mL

[†], Enhanced EPI vaccines at 9-months consist of measles-rubella (MR) and yellow fever (YF) vaccine; the Enhanced EPI vaccine at 15-months consists of MR vaccine.

[1] Conducted after consent obtained.

[2] Vital signs include heart rate and respiratory rate.

[3] Concomitant medication and vaccination history will be updated at study visits through Day 29.

[4]Field workers will visit homes as described in Section 5.4.

( ) As applicable

1 BACKGROUND AND SCIENTIFIC RATIONALE

1.1 Background

Meningococcal meningitis, caused by invasive strains of *Neisseria meningitidis*, is a major public health concern because of its considerable morbidity and mortality in sub-Saharan Africa. Case fatality during meningococcal meningitis epidemics can surpass 15%, and rates of permanent sequelae among meningitis survivors in Africa are twice as high as they are in high-income countries. Because of the fulminant clinical course of invasive bacterial meningitis and difficulties in access to care in the African meningitis belt, prevention by vaccination is the optimal way to reduce meningococcal meningitis morbidity and mortality. Before 2010, serogroup A meningococcal strains were routinely responsible for the majority (70-96%) of invasive meningococcal disease in sub-Saharan Africa.[1] An annual epidemic could be associated with an incidence of meningococcal disease which could range between 100-1000 cases per 100,000 persons in any given year.[2]

In 2001, the Meningitis Vaccine Project (MVP), a partnership between the World Health Organization (WHO) and PATH, was established to develop an inexpensive monovalent meningococcal serogroup A vaccine which could address the high burden of disease in sub-Saharan Africa.[3] MVP created the meningococcal serogroup A polysaccharide tetanus toxoid conjugate vaccine known as MenAfriVac, which was manufactured by Serum Institute of India Pvt. Ltd. (SIIPL, Pune, India). Progressive introduction of MenAfriVac since 2010 resulted in a substantial reduction in cases of serogroup A meningococcal disease, such that by 2011-13, the incidence had dropped to 0.02 cases per 100,000 persons;[4] by 2017, there were only two documented cases of serogroup A disease.[5]

Despite the introduction of the highly effective and affordable monovalent conjugate vaccine, regular large-scale epidemics due to serogroups C, W and X remain common in the African meningitis belt. Although serogroup C (NmC) was historically known for only causing infrequent and sporadic cases of meningitis, in recent years NmC has been the cause of an increasing number of epidemics. In 2013, a novel NmC clone (ST-10217)[6] emerged and has since been a source for a marked rise in the burden of serogroup C disease in sub-Saharan Africa.[7,8] In 2017 alone, the largest outbreak of serogroup C disease was recorded, causing over 14,000 cases in northern Nigeria.[9] Serogroup W (NmW, formerly referred to as W-135) was also previously associated with infrequent epidemics, but NmW clone (ST11/ET37) was the cause of a substantial outbreak during the Hajj in 2000,[10] and NmW has since been a major cause of meningococcal disease in sub-Saharan Africa.[11] Similarly, although serogroup X (NmX) was formerly recognized as a rare cause of meningitis cases, NmX is now another important cause of meningococcal disease in sub-Saharan Africa.[12]

No current polyvalent meningococcal conjugate vaccines are affordable at large scale for use in sub-Saharan Africa. Plus, there are no vaccines which address NmX.

An affordable and scalable pentavalent meningococcal conjugate vaccine (NmCV-5) has been developed by SIIPL, the manufacturer of MenAfriVac. NmCV-5 is designed to protect against serogroups A, C, W, Y and X. NmCV-5 contains meningococcal serogroups A and X polysaccharides conjugated to tetanus toxoid (TT) and serogroups C, W, and Y polysaccharides conjugated to Cross Reactive Material 197 (CRM_{197}) protein, a genetically detoxified mutant diphtheria toxin.[13]

1.1.1 Summary of Pre-Clinical Studies with NmCV-5

NmCV-5 underwent preclinical studies.[14] No safety concerns were observed and immune responses to all five serogroups were recorded. The United States Food and Drug Administration (U.S. FDA) reviewed the nonclinical studies, as part of an Investigational New Drug (IND) application, prior to the conduct of the first-in-human phase 1 trial. A summary of the completed pre-clinical studies is in **Table 1**.

Table 1: Completed pre-clinical studies of NmCV-5 candidates

Table 1: Completed pre-clinical studies of NmCV-5 candidates			
Study Title	**Site**	**Type**	**Animal Model**
5-week subcutaneous dose-ranging immunogenicity study of monovalent serogroup X conjugate (MenX-TT) with and without aluminum phosphate adjuvant	SIIPL	Immunogenicity; non-GLP	Swiss albino mice
7-week subcutaneous immunogenicity study of NmCV-5 with and within aluminum phosphate adjuvant	National Institute for Biological Standards and Control (NIBSC), London, UK	Immunogenicity; non-GLP	BALB/c mice
5-week intramuscular immunogenicity study of NmCV-5 formulations in comparison to commercial vaccine	SIIPL	Immunogenicity; non-GLP	New Zealand white rabbits
5-week intramuscular dose-ranging immunogenicity study of NmCV-5 (tox formulation) with and without aluminum phosphate adjuvant	SIIPL	Immunogenicity; non-GLP	New Zealand white rabbits
7-week intramuscular toxicity study of NmCV-5	MPI Research, Inc., 54943 North Main St., Mattawan, MI 49071-8353, USA	Toxicity & Immunogenicity; GLP	New Zealand white rabbits
Series of studies of 4-pyrrolidinopyridine (a byproduct of 1-cyano-4-pyrrolininopyridiniumtetrafluoroborate conjugation chemistry)	MPI Research, Inc., 54943 North Main St., Mattawan, MI 49071-8353, USA And BioReliance Corp., 14920 Broschart Rd., Rockville, MD, 20850-3349, USA	Byproduct toxicology & Mutagenicity; GLP	Rats, guinea pigs, prokaryotic & eukaryotic cells

1.1.2 Summary of Clinical Studies of NmCV-5

Phase 1, Adults in U.S.

A first-in-man phase 1 trial of NmCV-5 was performed at CVD (Baltimore, MD, U.S.A.) among healthy young American adults (published, NCT02810340).[15] This is the only clinical study of NmCV-5 registered with the U.S. FDA. In this phase 1 trial, 60 consenting subjects 18 to 45 years of age were randomly assigned in a 1:1:1 ratio to receive a single dose of either one of two formulations of NmCV-5 (adjuvanted with aluminum phosphate or non-adjuvanted) or the control vaccine, Menactra® (quadrivalent meningococcal polysaccharide diphtheria toxoid conjugate vaccine). The overall reported solicited reactogenicity (within 7-days post-immunization) was 65, 60, and 50% of subjects for the adjuvanted NmCV-5, non-adjuvanted NmCV-5, and control groups, respectively. Injection site pain was the most common local reaction and headache was the most common systemic reaction. Most solicited reactogenicity, for the 7 days following vaccination, was mild and all were self-limiting. Unsolicited AEs were also generally mild, and all resolved. There were no significant differences between the three vaccination groups in any solicited reaction. All three vaccination groups demonstrated immune responses, by rabbit-complement serum bactericidal antibody (rSBA) assay, four weeks after vaccination to the A, C, Y, and W serogroups, whereas only the adjuvanted and non-adjuvanted NmCV-5 vaccination groups demonstrated immune responses to serogroup X. The four-fold or greater rises in rSBA titers for serogroups A, C, Y, and W appeared comparable across treatment groups, and for serogroup X, in the NmCV-5 groups, appeared comparable to frequencies seen with the other serogroups for the same vaccines. Moreover, four weeks after immunization, for all five serogroups, all subjects who received non-adjuvanted NmCV-5 and 95 to 100% of subjects who received adjuvanted NmCV-5 had serum rSBA titers of 128 or higher.

Phase 2, Children in Mali

A phase 2 trial of NmCV-5 was performed at CVD-Mali (Bamako, Mali) among healthy Malian children aged 12-16 months and evaluated two doses of NmCV-5 (both adjuvanted and nonadjuvanted formulations given 3 months apart (published, NCT03295318).[16] In this trial, 375 Malian children were randomly assigned in a 2:2:1 ratio to receive two doses, three months apart, of either one of two formulations of NmCV-5 (adjuvanted with aluminum phosphate or non-adjuvanted) or the control vaccine, Menactra®. The overall frequency for systemic solicited reactogenicity was 4.0, 3.9, and 5.4%; the frequency of local solicited reactogenicity was 1.3, 3.0, and 0.7%. All solicited reactogenicity were reported as mild in severity, except for one instance of moderate fever; all solicited reactogenicity were self-limited. During the 28 days after receipt of the first dose, 26%, 25%, and 30% reported unsolicited AEs; none of these 122 AEs, other than 2 events of diarrhea in participants in the nonadjuvanted NmCV-5 group, were assessed by the investigator as being related to a trial vaccine. During the 28 days after receipt of the second dose, 12%, 16%, and 22% reported unsolicited AEs; none of these 58 AEs were assessed by the investigator as being related to a trial vaccine. At four weeks following the first dose of vaccine, seroresponse rates to all five serogroups were similar when comparing the adjuvanted and non-adjuvanted NmCV-5 groups; both NmCV-5 groups demonstrated higher

immune responses to all five serogroups when comparing to the control vaccine (**Table 2**). Based upon these data for safety and the lack of any apparent significant immune response benefits with aluminum phosphate adjuvant, a single-dose of the unadjuvanted NmCV-5 formulation was selected for advancement in clinical development.

Table 2: Percentage of subjects with seroresponse at 28-days following first dose in Malian Children

Table 2: Percentage of subjects with seroresponse at 28-days following first dose in Malian Children						
	Non-adjuvanted NmCV-5		Adjuvanted NmCV-5		Control	
Serogroup	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
A	146	99.3 (96.3, 100)	148	100 (97.5, 100)	72	97.3 (90.6, 99.7)
C	144	98.0 (94.2, 99.6)	145	98.0 (94.2, 99.6)	52	70.3 (58.5, 80.3)
W	143	97.3 (93.2, 99.3)	144	97.3 (93.2, 99.3)	67	90.5 (81.5, 96.1)
X	147	100 (97.5, 100)	146	98.6 (95.2, 99.8)	12	16.2 (8.7, 26.6)
Y	143	97.3 (93.2, 99.3)	146	98.6 (95.2, 99.8)	64	86.5 (76.5, 93.3)

Phase 3 trials for Licensure and WHO Pre-Qualification

The immediate goal for the clinical development of NmCV-5 is for WHO Pre-Qualification (WHO-PQ), to enable the vaccine to be used in the Meningitis Belt of sub-Saharan Africa. The NmCV-5 vaccine is registered with the National Regulatory Authority in India, under the Central Drugs Standard Control Organisation (CDSCO) office which is a component of the Drugs Controller General of India (DCGI). The most recent meeting between SIIPL, CDSCO, and the WHO-PQ team was held on October 9, 2020 to confirm the plan for regulatory registration in India (for licensure) as a requirement for WHO-PQ and allowing for the immediate use of the vaccine in sub-Saharan Africa. Since a longer-term goal for NmCV-5 is licensure in Europe, a scientific advisory meeting was held with the Paul Ehrlich Institute (PEI, Germany) on March 26, 2020 to validate the nonclinical, clinical, and chemistry, manufacturing, and control (CMC) programs for NmCV-5—a review and approval of our current WHO-PQ strategy. There are no immediate plans for U.S. licensure of NmCV-5, therefore the U.S. FDA does not have a role in the regulatory oversight of the continuing development of NmCV-5.

Three Phase 3 trials have been agreed upon as necessary for WHO-PQ, as reviewed by WHO and the WHO's Strategic Advisory Working Group of Experts (SAGE) working group on meningococcal vaccines. Two of these Phase 3 trials are already underway, and this study protocol represents the third Phase 3 trial necessary for WHO-PQ.

One Phase 3 study is being conducted in Mali (CVD-Mali) and The Gambia among 2-29-year-olds (NCT03964012). A total of 1800 eligible participants were randomized 2:1 to NmCV-5 or control vaccine (Menactra®) in each of the three age strata 18-29 years, 11-17 years & 2-10 years (with n=400 NmCV-5 recipients and n=200 control vaccine recipients in each age stratum). Each subject received a single dose of study vaccine and was followed up for 6 months post vaccination during which solicited reactions (for seven days), unsolicited AEs (28 days) and SAEs (until the end of study, i.e., 180 days after vaccination) were collected. A blood sample was collected at baseline (pre-vaccination) and at day 28 post-vaccination for immunogenicity

assessment by rSBA. This phase 3 African multi-site study is anticipated to be completed by end of 2021.

The second Phase 3 study is a lot-to-lot consistency study being conducted in India among 18-85-year-old adults (NCT04358731). The immune responses to three consecutively manufactured lots of NmCV-5 are to be statistically compared against the control vaccine (Menactra®). A total of 1640 subjects 18 to 85 years of age will be accrued contemporaneously across three age strata 18 to 29 years, 30 to 60 years, and 61 to 85 years. Within each age stratum, subjects will be randomly assigned in a 3:1 ratio to receive either NmCV-5 or control vaccine. The NmCV-5 subjects in the 18-29-year age group will be further randomized 1:1:1 to receive one of the three different lots of NmCV-5 (Lot A, B, or C). All the randomized subjects will receive a single dose of 0.5 ml of NmCV-5 or control vaccine on Day 1. Post vaccination site visits are planned on Days 8, 29 and 180; a telephone call follow-up visit will be completed at Day 85. This phase 3 lot-to-lot consistency study is also anticipated to be completed by end of 2021.

The third and last Phase 3 study, as agreed under the WHO-PQ strategy, is a study of NmCV-5 in the infant EPI schedule in sub-Saharan Africa—this is the present study described in this protocol. This study protocol is designed to provide evidence that concomitant vaccination with NmCV-5 will not significantly affect the immune responses of infants to their normally scheduled EPI vaccines. In sub-Saharan Africa, there are large differences between individual countries and their own EPI schedules. For example, MenAfriVac® is scheduled to be administered at 9 months in Mali, 12 months in The Gambia, 15 months in Burkina Faso, and at 18 months in Ghana. Because NmCV-5 will eventually be adopted within each respective country according to their own existing EPI schedules, we have specifically designed this study to provide information at two distinct timepoints, 9 months and 15 months. The WHO-PQ quadrivalent meningococcal conjugate vaccine MenACWY-TT (Nimenrix®, manufactured by Pfizer) is to be the control comparator vaccine to NmCV-5. MenACWY-TT is approved for use in infants as young as 6 weeks of age. Menactra® is approved for use in children 1 year of age and older, thus cannot be used as the comparator vaccine for infants age 9 months. WHO supports the evaluation of the age ranges of 9 months and 15 months under which NmCV-5 is intended to be adopted by stakeholder countries in the Meningitis Belt.

Table 3: Current EPI Schedule in Mali

Table 3: Current EPI Schedule in Mali					
Birth	**6 weeks**	**10 weeks**	**14 weeks**	**9 months**	**15 months**
BCG OPV	OPV DTwP Hib HepB PCV Rotavirus	OPV DTwP Hib HepB PCV Rotavirus	OPV DTwP Hib HepB PCV Rotavirus IPV	Measles only Yellow fever MenA	(none*)
BCG, Bacillus Calmette–Guérin vaccine; OPV, oral poliovirus vaccine; DTwP, diphtheria-tetanus-pertussis vaccine; Hib, Haemophilus influenzae type b vaccine; HepB, hepatitis B virus vaccine; PCV, pneumococcal conjugate vaccine; IPV, inactivated poliovirus vaccine *Mali is beginning to implement a second dose of measles-containing vaccine within the EPI schedule in certain locations, but this is not yet widespread among the general population					

The study design of this Phase 3 EPI study requires two notable modifications to the current standard EPI schedule in Mali. The current Mali EPI schedule consists of a measles only vaccine, yellow fever vaccine, and MenA vaccine at 9 months of age; there is no 15 months of age EPI vaccine visit and typically only a single dose of a measles-containing vaccine is administered. However, to satisfy the conditions for WHO-PQ, study participants will receive two doses of a measles-containing vaccine, at 9-months and 15-months. Furthermore, the WHO-PQ non-inferiority evaluation must include an assessment of the potential effect on rubella vaccine responses. In order to satisfy the conditions for WHO-PQ, the measles-containing vaccine must contain rubella vaccine. Therefore, the study design will include 2-doses of a measles and rubella-containing vaccine (measles and rubella vaccine [MR]; the first dose will be at 9 months of age (per the current EPI in Mali) and the second at 15 months of age. These modifications to the standard Malian EPI schedule provide a level-of-care that is higher than the current standard-of-care for the general population. Within the context of this study, we will refer to this as an "enhanced" EPI schedule.

Table 4: "Enhanced" EPI Schedule for study participants

"Enhanced" EPI Schedule for study participants					
Birth	**6 weeks**	**10 weeks**	**14 weeks**	**9 months**	**15 months**
No change from existing EPI schedule in Mali	*No change from existing EPI schedule in Mali*	*No change from existing EPI schedule in Mali*	*No change from existing EPI schedule in Mali*	Measles-Rubella Yellow fever (MenConjugate)*	Measles-Rubella (MenConjugate)*
*a pentavalent (NmCV-5) or quadrivalent (MenACWY-TT) meningococcal conjugate vaccine will be administered once, either at 9 months or at 15 months					

1.2 Scientific Rationale

1.2.1 Purpose of Study

This phase 3 study will evaluate a single dose of NmCV-5 at two time points in the EPI calendar where it is most likely to be used (i.e., at 9 months and 15 months of age). The comparator vaccine, MenACWY-TT is licensed as a single-dose vaccine for this age group. The primary aim is to determine whether a single dose of NmCV-5 given at 9 or 15 months is non-inferior to a single dose of MenACWY-TT in mounting immune responses against *N. meningitidis* serogroups A, C, W, and Y one month (28 days) after vaccination. Secondary aims (SA) include: to demonstrate that administration of NmCV-5 does not interfere with EPI vaccine responses (measles-rubella, yellow fever, measles booster) and to demonstrate that NmCV-5 elicits immune responses against serogroup X.

1.2.2 Study Population

The study will be conducted in healthy infants aged 9 and 15 months who reside in Bamako, Mali.

1.3 Potential Risks and Benefits

1.3.1 Potential Risks

Risks from NmCV-5

This is an experimental meningococcal vaccine which is not locally approved. Among toddlers that have received intramuscular (IM) doses of NmCV-5, reactions over the 7 days after vaccination included injection site pain, redness, and swelling; there was also irritability, drowsiness, anorexia, vomiting, and fever. These local and systemic reactions were not severe, and all resolved without any permanent consequences. No immediate allergic reactions have been observed but this is a theoretical risk with all vaccines. Persons with a history of any severe allergic reactions to components in the vaccine (e.g., CRM or TT) are contraindicated from receipt of NmCV-5. Since this is an experimental vaccine, there is a possibility of side effects that are not yet known, including rare allergic reactions that could be severe. Participants will be observed for any immediate reactions for 30 minutes after being vaccinated.

Risks from Comparator Vaccine, MenACWY-TT

This is a locally licensed meningococcal vaccine, approved for infants as young as 6 weeks of age. The very common (>10%) side effects of this vaccine include pain, swelling, and redness at the injection site, and fever, tiredness, headache, drowsiness, loss of appetite, and irritability. Other common (<10%) side effects include injection site bruising, diarrhea, vomiting, nausea, and rash. The uncommon (<1%) side effects of this vaccine may include crying, itching, feeling dizzy, aching muscles, arm and leg pain, generally feeling unwell, difficulty sleeping, lump at the injection site, and limb swelling. Persons with a prior severe allergic reaction to this vaccine or to a component of this vaccine (e.g., TT) are contraindicated from receipt of MenACWY-TT.

Risks from Measles-Rubella Vaccine

This is a WHO-PQ vaccine, approved for infants as young as 6 months of age. The common side effects of this vaccine include fever (<15%), transient rashes (5%), transient lymphadenopathy (5%). Other possible side effects may include coryza, cough pharyngitis, headache, conjunctivitis, nausea, vomiting, lymphadenopathy, and joint pain. Febrile seizures are rare and may occur with a frequency of 1 case per 3000 doses administered. Immune thrombocytopenic purpura, a disorder affecting blood platelet counts, are rare and may occur with a frequency of 1 case per 40,000 doses administered. Anaphylactic reactions are another very rare event which may occur with a frequency of 1.8 cases per million doses administered. Because this is a live, attenuated virus vaccine, the vaccine is contraindicated in persons who are severely immunocompromised as a result of congenital disease, HIV infection with immunocompromise, advanced leukemia or lymphoma, serious malignant disease, or treatment with high-dose steroids, alkylating agents or anti-metabolites, or in persons who are receiving immunosuppressive therapeutic radiation. The vaccine may contain traces of neomycin, so history of anaphylactic reactions to neomycin and history of severe allergic reaction to any component of the vaccine are absolute contraindications. There are extremely rare reports of

hypersensitivity reactions in persons allergic to cow's milk. Such individuals should not receive the vaccine.

Risks from Yellow Fever Vaccine

This is a locally licensed vaccine, approved for infants as young as 6 months of age and is the same vaccine used in the current Mali EPI program. The common side effects of this vaccine include headache (33%), myalgia (25%), malaise (19%), low-grade fever (15%), chills (11%), and injection site pain and swelling. Anaphylactic reactions are very rare and may occur at 0.8 cases per 100,000 doses administered. The live, attenuated vaccine is associated with very rare vaccine-associated neurologic disease (YF-AND) which can be fatal and has been observed with persons <6 months of age, older persons >60 years of age, and persons with underlying immunosuppressive conditions. Vaccine-associated viscerotropic disease (YF-AVD) is another very rare event which can mimic natural infection with yellow fever virus, it may occur at 0.4 cases per 100,000 doses administered. An increased risk of YF-AVD is associated with older age (>60 years), history of thymus disease, or thymectomy. The vaccine is contraindicated for persons with a history of severe allergic reactions to any of the vaccine components, including eggs or egg products (persons who can eat eggs may receive the vaccine), chicken proteins, gelatin, or latex rubber (from the vial stopper). The vaccine is also contraindicated for persons with a thymus disorder that is associated with abnormal immune cell function (e.g., thymoma or myasthenia gravis), HIV infection, and persons who are severely immunocompromised.

Risks with Blood Draws

Drawing blood may cause pain, bruising, lightheadedness, fainting, bleeding, and rarely infection. The research team will use gloves and sterile equipment and will cleanse the site of blood draw with alcohol prior to blood draw to reduce the risk of infection.

Risk to Confidentiality

We will collect personal health information (PHI) on all participants and this sensitive information is intended to be maintained as confidential, within the limits of the law. We will also take photographs of the children as part of ensuring that study participants can be re-identified on subsequent visits, this is a locally accepted practice to help the study team match study participants with their identify and helps to ensure the research records are accurate. However, there is a risk for unauthorized access this PHI. Paper research records will be kept in locked files or maintained in locked rooms in the research area. Electronic research records will be password protected. Only authorized study personnel who are involved in the study will be allowed to have access to this PHI. Any publication from this study will not use information which will reveal the identities of individuals.

Risk with Delayed Meningococcal Vaccination

Some study participants will be randomized to delay the receipt of meningococcal vaccination to 15-months. The monovalent MenA vaccine is normally administered at the 9-month EPI visit. The local epidemiology of serogroup A meningococcal disease has been nearly eliminated since

the beginning of routine MenA EPI vaccination. Therefore, there is a very small risk that the delayed vaccination will present a window of vulnerability to invasive serogroup A meningococcal disease. Furthermore, WHO recommends MenA vaccination may be administered anytime between 9 and 18 months, so this does not represent a delay according to WHO's recommendation.

Unknown Risks

The study vaccine is experimental. There is a chance that there are additional risks that we cannot foresee right now. Study personnel will inform study participants if there is any significant new information regarding the risks or benefits of this study.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by US Law. This web site will not include information that can identify subjects. This web site will include a summary of the results in a tabular format including participant flow; demographic and baseline characteristics; primary outcomes, as well as results of any scientifically appropriate statistical tests; and adverse event information.

There may be other risks, discomforts, or side effects that are unknown at this time.

1.3.2 Potential Benefits

All study participants will be given the opportunity to receive "enhanced" EPI vaccination. There should be improved protection against measles with the receipt of two doses of a measles-containing vaccine. The receipt of this vaccine, containing rubella, also benefits the infant through protection from rubella. Instead of the monovalent meningitis vaccine (MenAfriVac), participants will receive either the pentavalent NmCV-5 vaccine or the quadrivalent MenACWY-TT vaccine. There is the possible benefit of being afforded protection against some of the additional meningococcal serogroups which are known to cause invasive disease in sub-Saharan Africa. All study participants will have close monitoring with scheduled follow-up visits with the research clinic and this close follow-up may also provide a benefit to the infant through improved access to medical care.

2 STUDY DESIGN, OBJECTIVES AND ENDPOINTS OR OUTCOME MEASURES

2.1 Study Design Description

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). If "enhanced" EPI vaccinations are declined or not available, infants will be referred to local clinic for standard EPI vaccination.

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 5: 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.

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. Study vaccinations will be administered in a monitored environment where treatment for immediate reactions such as anaphylaxis, will be available. Study physicians will be onsite during all vaccinations, and subjects will be observed for 30 minutes following vaccination. The rabbit complement-dependent serum bactericidal antibody (rSBA) assay will be performed at UK Health Security Agency (UKHSA) in Manchester, UK, an international reference laboratory for meningococcal vaccine immunology. UKHSA performed the assays for all trials of MenAfriVac as well as the Phase I and II trials of NmCV-5. Immunological assays for measles, rubella, and yellow fever will be performed at VisMederi in Siena, Italy. .

2.2 Study Objectives

2.2.1 Primary

- 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 non-inferior 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.

2.2.2 Secondary

- To assess the safety and tolerability of a single dose of NmCV-5 or MenACWY-TT, when given concomitantly with routine vaccines.
- 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 immune responses to EPI vaccines (measles-rubella, yellow fever, measles booster) when co-administered with NmCV-5 (at either 9 or 15 months of age) compared to the immune responses when co-administration with MenACWY-TT (at either 9 or 15 months).
- To assess other clinically significant immune response indicators elicited by a single dose of NmCV-5, given concomitantly with routine vaccine, as compared to those elicited by MenACWY-TT.

2.2.3 Tertiary

- To assess the safety of a single dose of NmCV-5 or MenACWY-TT through 2 years of follow-up after meningococcal vaccination.
- To assess the persistence of the immune responses at 6 months and 2 years after meningococcal vaccination.

2.2.4 Exploratory

- To compare the immune responses of the 9-month and 15-month group against each of the five meningococcal serogroups at Day 29.

2.3 Study Endpoints or Outcome Measures

2.3.1 Primary

Primary Outcome Measures - Immunogenicity

- The percentage of participants with seroprotective response (rSBA antibody titers ≥ 8) against each meningococcal serogroup A, C, W, X 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.

2.3.2 Secondary

Secondary Outcome Measures - Meningococcal Response

- 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.
- 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 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*.
- Number and proportion of participants with rSBA titers ≥ 128 at 28 days after a single dose of meningococcal vaccine.

Secondary Safety Endpoints

- Any 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.

Secondary Immunogenicity Endpoints

- 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 ≥ 1:10.*

2.3.3 Tertiary

Tertiary Safety Endpoints

- All SAEs, reported through 2 years of follow-up or during the entire study period.
- 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.

2.3.4 Exploratory

Exploratory Immunogenicity Endpoints

- 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.

3 STUDY INVERVENTION/INVESTIGATIONAL PRODUCT

3.1 Study Product Description

3.1.1 Formulation, Packaging, and Labeling

NmCV-5 Vaccine: Active Product(s) and Components

The NmCV-5 investigational vaccine, manufactured by SIIPL, is formulated as a lyophilized powder containing meningococcal serogroups A and X polysaccharides conjugated to TT and meningococcal serogroups C, W and Y polysaccharides conjugated to CRM_{197} protein. The vaccine is to be reconstituted with normal saline just prior to administration. The NmCV-5 lyophilized powder component contains sucrose, sodium citrate and trometamol as excipients. This vaccine is presented as a freeze-dried powder in a single-dose vial.

0.9% Sodium Chloride (normal saline) is the diluent used to prepare NmCV-5 and it is provided with vaccine. The diluent is a clear, colorless liquid. For the preparation of the NmCV-5 from a single dose vial, the contents are contemporaneously reconstituted with 0.63 ± 0.03 mL of provided diluent (normal saline). After reconstitution, a single 0.5 mL dose of NmCV-5 injectable solution will have the following composition: 5 mcg of weight for each of the five polysaccharides (A, C, Y, W, and X), tetanus toxoid, CRM_{197}, sucrose, sodium citrate, TRIS (trometamol), and sodium chloride.

MenACWY-TT: Comparator Vaccine

The comparator vaccine is the licensed meningococcal ACWY-TT conjugate vaccine, manufactured by Pfizer. MenACWY-TT is supplied as a single-dose vial of lyophilized powder containing meningococcal serogroups A, C, W, and Y polysaccharides conjugated to TT; the vaccine vial also contains sucrose and trometamol as excipients. The vaccine is to be reconstituted with the solvent, consisting of sodium chloride and water for injection, from a pre-filled single-use syringe. The reconstituted MenACWY-TT vaccine contains: 5 mcg of weigh for each of the four polysaccharides (A, C, W, and Y), tetanus toxoid, sucrose, trometamol, and sodium chloride.

Measles and Rubella Vaccine

The MR vaccine is WHO-PQ and manufactured by SIIPL. MR is prepared from live, attenuated Edmonston-Zagreb measles virus and Wistar RA27/3 rubella virus propagated in human diploid cells. MR is supplied as a single-dose vial of lyophilized powder, when reconstituted with the provided diluent in the vaccine package, each dose of 0.5 mL contains ≥1000 $CCID_{50}$ (cell culture infective dose 50%) measles virus and ≥1000 $CCID_{50}$ rubella virus.

Yellow Fever Vaccine

The YF vaccine (Stamaril®, manufactured by Sanofi Pasteur) is WHO-PQ and will be acquired through the EPI program. YF was prepared from live, attenuated 17D yellow fever virus propagated in Specific Pathogen Free (SPF, specifically avian Leukosis virus free) chick

embryos. YF is supplied as lyophilized powder in vials with solvent containing lactose, sorbitol, histidine, alanine, and sodium chloride. Each reconstituted dose of YF contains ≥1000 LD50 (historically the units refer to a weanling mouse intracerebral lethal dose 50%) yellow fever virus.

3.1.2 Product Storage and Stability

NmCV-5

The NmCV-5 vaccine including diluent should be stored at 2°C to 8°C. Do not freeze. Following reconstitution with normal saline, it is recommended to be administered immediately and no more than two hours and may be kept at room temperature.

MenACWY-TT

MenACWY-TT vaccine including solvent should be stored at 2°C to 8°C. Do not freeze. A single dose vial (type I glass vial with butyl rubber stopper) containing lyophilized vaccine powder and a pre-filled syringe with solvent is provided for each dose of vaccine. Following reconstitution with solvent, it is recommended to be administered immediately.

Measles and Rubella Vaccine

MR vaccine including diluent should be stored in the dark at 2°C to 8°C. It is important to protect both the freeze-dried and reconstituted vaccine from the light. For long-term storage of the freeze-dried vaccine, -20°C (-15°C or colder) is recommended. The diluent should not be frozen but should be kept at refrigeration, 2°C to 8°C. Following reconstitution with diluent, the vaccine should be used within 2 hours but may be stored in the dark at 2°C to 8°C for no longer than 6 hours.

Yellow Fever Vaccine

YF vaccine including solvent should be stored at 2°C to 8°C. Do not freeze. Following reconstitution with solvent, it is recommended to administer the dose within six hours and stored at 2°C to 8°C.

3.2 Acquisition/Distribution

The study product NmCV-5 and MR vaccine will be provided by SIIPL to the clinical site. The control vaccine MenACWY-TT will be acquired from a commercial source by Centre pour le Développement des Vaccins, Mali (CVD-Mali). The YF vaccine will be acquired from the Mali EPI program. Detailed information regarding the acquisition and distribution of the study product will be included in the Manual of Procedures (MOP).

3.3 Dosage/Regimen, Preparation, Dispensing and Administration of Study Intervention/Investigational Product

NmCV-5: Active Product(s)

NmCV-5 is reconstituted by transferring the entire volume of diluent from ampoule into the lyophilized vaccine vial. After reconstitution the vaccine must be used as soon as possible but not later than two hours, during which time it may be kept at room temperature but must not be frozen. 0.5 mL is then injected to the subject intramuscularly. The preferred site of administration is the anterolateral aspect of the thigh.

MenACWY-TT: Comparator Vaccine

MenACWY-TT must be reconstituted by adding the entire content of the pre-filled syringe of solvent to the vial containing the lyophilized powder vaccine. This reconstituted vaccine should be maintained at room temperature. Following reconstitution, it is recommended to be administered promptly within two hours. Approximately 0.5 mL of the contents is then injected to the subject intramuscularly. The preferred site of administration is the anterolateral aspect of the thigh.

Measles and Rubella Vaccine

MR should be reconstituted only with the entire diluent supplied. The reconstituted vaccine should be used immediately but may be stored in the dark at 2°C to 8°C for no longer than 6 hours. All of the contents from the reconstituted vaccine vial will be drawn. A single dose of 0.5 mL should be administered by deep subcutaneous injection into the deltoid.

Yellow Fever Vaccine

YF should be reconstituted only with the entire solvent supplied. The reconstituted vaccine should be used immediately but may be refrigerated and stored at 2°C to 8°C for up to 6 hours. A single dose of 0.5 mL should be administered by subcutaneous route into the deltoid.

3.4 Pre-determined Modification of Study Intervention/Investigational Product for an Individual Subject

Prior to vaccination, subjects must be determined to be eligible for study vaccination and it must be clinically appropriate in the judgement of the investigator to vaccinate. Eligibility review will include a specific assessment for whether the subject has received a meningococcal vaccine. Concomitant administration of routine EPI vaccines is to be documented as concomitant medications and are not considered study vaccines.

3.5 Accountability Procedures for the Study Intervention/Investigational Product(s)

The study product NmCV-5 and MR will be provided by SIIPL to the clinical site. The control vaccine MenACWY-TT will be acquired from a commercial source. The YF vaccine will be

acquired from the Mali EPI program. Once received, the study products will be stored in and dispensed from the CVD-Mali Investigational Pharmacy. Instructions on study product destruction will be included in the MOP.

The Investigator is responsible for ensuring that a current record of product disposition is maintained, and product is dispensed only at an official study site by authorized personnel as required by applicable regulations and guidelines. Records of product disposition consist of the date received, date administered, quantity administered, and the subject number to whom the drug was administered.

The Investigational Pharmacist will be responsible for maintaining accurate records of the shipment and dispensing of the investigational product. The pharmacy records must be available for inspection by the DMID monitoring contractors and is subject to inspection by a regulatory agency as applicable at any time. An assigned Study Monitor will review the pharmacy records.

Unused reconstituted investigational product vials will be stored at 2ºC to 8ºC in the Investigational Pharmacy until clinical trial accountability is completed. At study termination, all unused investigational product will be disposed in accordance with the MOP following complete drug accountability and monitoring.

4 SELECTION OF SUBJECTS AND STUDY ENROLLMENT AND WITHDRAWAL

4.1 Eligibility Criteria

4.1.1 Subject Inclusion Criteria

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

1. Male and female children between 9 months and 11 months old inclusive.
2. Parent(s)/legal guardian(s) have provided written informed consent, after the nature of the study has been explained according to local regulatory requirements.
3. The investigator believes that their parent(s)/guardian(s) will be available for all the subjects visits and will comply with the requirements of the protocol (e.g., timely reporting of adverse events).
4. Individual is in good health as determined by medical history, physical examination, and clinical judgement of the investigator. (*Note: the physical examination may have been performed on a separate screening day and will be considered valid if within 14 days of enrollment*)
5. Individual has completed their local infant EPI vaccines, not including 9-month EPI vaccines (at the 9-month visit) or 15-month EPI vaccines (at the 15-month visit). A birth dose of oral polio vaccine is not required.

4.1.2 Subject Exclusion Criteria

In order to participate in this study, all subjects must meet NONE of the exclusion criteria described.

1. History of receipt of any meningococcal vaccine.
2. Has received a measles-containing vaccine.
3. Current or previous, confirm or suspected disease caused by *N. meningitidis*.
4. Household contact with and/or intimate exposure to an individual with any laboratory confirmed *N. meningitidis* infection within 60 days of enrolment or study vaccination (for the 15-month age group).
5. History of severe allergic reactions after previous vaccinations or hypersensitivity to any study vaccine component including tetanus, diphtheria and mutant diphtheria toxoid (CRM_{197}).
6. Acute or chronic, clinically significant pulmonary, cardiovascular, metabolic, neurological, hepatic, or renal functional abnormality, as determined by medical history or physical examination.

7. Any confirmed or suspected condition with impaired or altered function of the immune system (e.g., immunodeficiency, autoimmune conditions, malnutrition).
8. Have any bleeding disorder which is considered a contraindication to intramuscular injection or blood draw.
9. Severe acute malnutrition. *Note: a weight-for-length Z-score of less than –3 satisfies this exclusion criteria*.
10. History of either hepatitis B or hepatitis C virus infection, human immunodeficiency virus infection, or hereditary immunodeficiency.
11. Presence of major and clinically significant congenital defects.
12. Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within three months prior to the study vaccination or planned use throughout the study period (for corticosteroids, this means prednisone, or equivalent, ≥ 0.5 mg/kg per day. Inhaled, intranasal, and topical steroids are allowed).
13. Administration of blood, blood products and/or plasma derivatives or any parenteral immunoglobulin preparation in the past 3 months or planned use throughout the study period.
14. Administration of any vaccine within 14 days prior to enrolment in the study or planned administration of any vaccine within 14 days before or after study vaccination.
15. Use of any investigational or non-registered drug or vaccine within 28 days prior to the administration of study vaccine or planned during the study.
16. Malaria infection as confirmed by a Rapid Diagnostic Test. *Note: subjects positive at screening may be treated for malaria as per national guidelines outside the study, and if the subject remains eligible, vaccinated no earlier than 5 days after completing treatment.*
17. Individuals who are close family member* of individuals conducting this study. **defined as a child with direct genetic relationship to a member of the study team*.
18. Have experienced a moderate or severe acute infection and/or fever (defined as temperature ≥ 37.5°C) within 3 days prior to enrolment or study vaccination.
19. Have received systemic antibiotic treatment within 3 days prior to enrolment or study vaccination.
20. Non-residence in the study area or intent to move out within six months.
21. Any condition which, in the opinion of the investigator, might pose additional risk to the subject due to participation in the study.

4.2 Withdrawal from the Study, Discontinuation of Study Product, or Study Termination

4.2.1 Withdrawal from the Study or Discontinuation of the Study Product

Parent(s)/legal guardian(s) may voluntarily withdraw their consent for study participation at any time without penalty or loss of benefits to which they are otherwise entitled.

An investigator may also withdraw a subject from receiving the study product for any reason. Follow-up safety evaluations will be conducted if the subject agrees. If a subject withdraws or is withdrawn prior to completion of the study, the reason for this decision must be recorded in the electronic case report forms (eCRFs).

The reasons, might include, but are not limited to the following:

- Subject no longer meets eligibility criteria
- Subject meets halting criteria (reference to Section 7.6.1)
- Study has been halted
- Subject becomes noncompliant
- Medical disease or condition, or new clinical finding(s) for which continued participation, in the opinion of the investigator might compromise the safety of the subject, interfere with the subject's successful completion of this study, or interfere with the evaluation of responses
- Subject lost to follow-up
- Subject does not receive meningococcal study product as part of step 2 randomization at the 15-month visit, due to the study having already filled the total enrollment number.
- Determined by a physician’s discretion to require additional therapy not indicated in the protocol to ensure subject’s health and well-being (or treatment failure, if applicable)

The investigator should be explicit regarding study follow-up (e.g., safety follow-up) that might be carried out despite the fact the subject will not receive further study product. If the subject consents, every attempt will be made to follow all AEs through resolution. The procedures that collect safety data for the purposes of research must be inclusive in the original informed consent or the investigator may seek subsequent informed consent using an IRB/IEC-approved consent form with the revised procedures.

The investigator will inform the subject that already collected data will be retained and analyzed even if the subject withdraws from this study.

4.2.2 Subject Replacement

Subjects who withdraw, or are withdrawn from this study, or are lost to follow-up after signing the informed consent form (ICF) and either before or after administration of the study product will not be replaced.

4.2.3 Participants who are randomized into Group 2 (15-month) but are not vaccinated with a randomized meningococcal vaccine

Subjects that are randomized to Group 2 (with Step 1 randomization) and present to the 15-month of age visit that do not have second-step randomization because the target enrollment sample size has been fulfilled will be offered "enhanced" EPI vaccination (i.e., MR vaccine and MenACWY-TT vaccine in open-label fashion) but will not receive further scheduled follow-up visits in the study.

4.2.4 Study Termination

If the study is prematurely terminated by the sponsor, any regulatory authority, or the investigator for any reason, the investigator will promptly inform the study subjects and assure appropriate therapy or follow-up for the subjects, as necessary. The investigator will provide a detailed written explanation of the termination to the IRB/IEC.

5 STUDY PROCEDURES

Complete study schedule details listed by type of visit are described below.

5.1 Screening

Community Permission

Given the local social structure, once the ethical and regulatory approvals are in place, community meetings will be organized to present the study to the communities where the site team plans to conduct the study. These meetings will be organized following these procedures:

- The informed consent forms will be translated into the local language and recorded through a certified process;
- Community meetings will be scheduled with the elders, the religious representatives, the social leaders and village chiefs in each community where the study will be conducted. At these meetings, the study will be explained in detail and, when applicable, the recording of the consent will be played;
- The study will be discussed and the study team will answer any questions. The community leaders will review the information and confirm their permission for the conduct of the study and a signed list of presence of attendance list will be obtained.
- The leaders or a local crier will announce the study and direct interested persons to the site. The study site team will then be allowed to start recruitment activities and approach potential subjects.
- As part of the ongoing consent of the community, an end of study community meeting will be conducted to communicate the overarching study results. If new information arises with regards to the safety or possible benefit (e.g., failure of the NmCV-5 to achieve non-inferior immunogenicity) of the study, then an ad hoc community meeting will be conducted to communicate this new information.

Site Recruitment

The site will develop a study specific recruitment plan and will use several approaches for recruitment:

- The list of children 7-9 months of age with their contact information will be obtained from the demographic surveillance system. Participants may also be enrolled from the greater Bamako area through community engagement activities that may include meetings with local health care providers and leaders. Community liaisons/field workers will visit each household and inform parents/guardians about the study. If interested, the parent/guardian will be directed to visit the site clinic for more information.
- The study team will collaborate with the community clinics to search for potential subjects when they come for their EPI vaccinations. Study staff will be present at the community clinics during vaccination days. If interested, the parent/guardian will be

referred to the site staff for information on the study.

Individual Informed Consent

"Informed consent" is the voluntary agreement of an individual or his/her legal guardian to participate in research. Consent must be given with free will of choice, and without inducement. The individual must have sufficient knowledge and understanding of the nature of the proposed research, the anticipated risks and potential benefits, and the requirements of the research to be able to make an informed decision. Informed consent of the parents/guardians following local IRB/EC guidance must be obtained before conducting any study-specific procedures.

The informed consent process will be conducted on potential study participants as early as 9 months of age. At this stage, the parent(s)/guardian(s), based on their interest in the study will decide if they agree to potentially delay their child's meningococcal vaccine dose until the child's 15-month EPI visit. If they agree, the subject's parent(s)/guardian(s) will be asked to sign the informed consent document. Upon this initial consent, a first step randomization (Step 1 Randomization) will be performed which will determine whether the infant will be enrolled into the study at the 9-month visit or at the 15-month EPI visit. 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.

This process of obtaining informed consent for study participation should be documented in the source documents. Two originals of the informed consent form should be signed and dated. One original will be given to the parent(s)/guardian(s) and one original will be kept at the site. The adult literacy rate in Mali is relatively low, only ~25% of adults can read French. The informed consent is presented in entirety in the local language (in the major local dialects) by audio recording. Furthermore, if the subject's parent(s)/guardian(s) is unable to read, an impartial witness will be present during the entire informed consent process and discussion. An impartial witness is defined as a person who is independent from study conduct, who cannot be unfairly influenced by those involved with the study, who attends the informed consent process if the subject's parent/guardian cannot read, and who reads the informed consent form and any other written information supplied to the parent/guardian.

After the written informed consent form and any other written information to be provided to subject's parent/guardian, is heard or read and explained to the subject's guardian/parent and after the subject's parent/guardian has verbally consented to the subject's participation in the study and, if capable of doing so, has signed the informed consent form, the witness will sign and personally date the consent form. For persons unable to read or write, an "X" or other marking is a currently locally acceptable signature. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject's parent/guardian and that informed consent was freely given by the subject's parent/guardian.

After informed consent, the following procedures will be performed as part of the Screening Visit:

- Entry of the subject identification (ID) into a screening log
- Confirm the individual meets all inclusion and no exclusion criteria
- Collect and review demographic information, including age, gender, race, and ethnicity
- Collect and review medical history and including review of systems
- Perform a general physical examination including assessment of height, weight, heart rate, respiratory rate, and axillary body temperature
- Collect and review prior/concomitant medications and prior vaccinations
- Obtain consent for enrollment
- Perform Step 1 Randomization

5.2 Enrollment

At Visit Day 1, upon confirmation of ongoing informed consent and the eligibility of the subject, there will be a second step randomization (Step 2 Randomization) at a 2:1 ratio to determine whether the infant will receive experimental vaccine or active control vaccine, as a blinded study product. This second step randomization will occur on the day subjects are to receive their first study injection (at 9 or 15 months of age based on Step 1 Randomization), after confirmation of eligibility and immediately prior to injection.

The unblinded designated personnel will be provided with the randomization list 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 list in a secure place.

If for any reason, after signing the informed consent form, the subject (who has passed screening) fails to be randomized, the reason for not being randomized should be recorded in source documents and eCRFs. For the 15-month groups, if the target Step 2 randomized sample size of 600 has been achieved, then the study will be closed to further second step randomizations. Study participants that are unable to receive meningococcal study product with step 2 randomization, due to closure to further enrollments, will be provided quadrivalent meningococcal conjugate vaccine (open-label) and will not be required to have further study follow up.

Visit #1 (Day 1 for Group 1)

- Confirm informed consent
- Review for any changes to the medical history (if not same day as screening), including review of systems.
    - Review of systems: an interview that queries the subject's parent/guardian as to any clinical findings the subject has experienced across each organ system (if not

same day as screening). The questions tend to be grouped by system organ class and are intended to remind the parent/guardian of any forgotten or medical conditions that may be relevant.

- Review of prior/concomitant medications and prior vaccinations (if not same day as screening)
- Perform a general physical examination (if not same day as screening, must be within 14 days of screening) including measurement of axillary body temperature, height, weight, and resting vital signs: heart rate and respiratory rate. The height and weight need to be recorded in source documents or eCRFs. *Note: If the subject's* axillary *body temperature is ≥37.5°C, vaccination must be postponed until three days after the fever has resolved. Vaccination is also postponed for any clinically significant acute infection and/or systemic antibiotic use within 3 days.*
- Perform Rapid Diagnostic Test for malaria. In case of a positive result, vaccination should be postponed until at least five days after completing treatment as per national guidelines.
- Study personnel will take a photo of the subject and his/her parent/guardian for the study identification card. This study identification card will be given to each subject's parent/guardian and will have phone numbers with 24 hours access in case of emergency.
- Perform Step 2 Randomization. Unblinded staff will perform Step 2 Randomization.
- For participants randomized into Group 1:
    - Collect blood sample (approximately 5 mL) for serology testing prior to vaccination.
    - Administer blinded study meningococcal vaccine, according to randomization assignment. The preparation and administration of study meningococcal vaccine will be performed by unblinded staff.
    - After vaccination, the subject will be observed for at least 30 minutes for any immediate post-vaccination reactions, with appropriate medical treatment readily available in case of a rare anaphylactic reaction following the administration of vaccines. Solicited local and systemic AEs, any unsolicited AEs, vital signs and axillary body temperature will be recorded. All safety data collected within 30 minutes post-vaccination should be recorded in the subject's source documents or eCRFs.
    - The participant's infant immunization card and medical record will be updated to indicate the receipt of a serogroup A meningococcal vaccine.
    - Schedule Visit 2 approximately 7 days after vaccination
    - Field workers will visit participant homes each day for the next 4 to 7 days as described in Section 5.4.
- For participants randomized into either Group 1 or Group 2, a measles-rubella-containing vaccine and yellow fever vaccine will be administered, according to the "enhanced" EPI

schedule. *Note: these administered "enhanced" EPI vaccines are also to be recorded on the participant's infant immunization card and medical record.*

- For participants randomized into Group 2 (the 15-month group), they will return in 6 months for Visit 1B for the study meningococcal vaccine randomization (Step 2) and vaccination. For participants randomized into the 15-month group and not randomized or enrolled to receive the study meningitis vaccine, refer to Section 4.2.3.

Group 2 only, Visit #1B (at 15 months of age), Study Day 1

- Confirm ongoing informed consent
- Confirm subject ID and the individual continues to meet all inclusion and no exclusion criteria.
- Review for any changes to the medical history, including review of systems.
    - Review of systems: an interview that queries the subject's parent/guardian as to any clinical findings the subject has experienced across each organ system. The questions tend to be grouped by system organ class and are intended to remind the parent/guardian of any forgotten or medical conditions that may be relevant.
- Review of prior/concomitant medications and prior vaccinations
- Perform a general physical examination including measurement of axillary body temperature, height, weight, and resting vital signs: heart rate and respiratory rate. The height and weight need to be recorded in source documents or eCRFs. *Note: If the subject's* axillary *body temperature is ≥37.5°C, vaccination must be postponed until three days after the fever has resolved. Vaccination is also postponed for any clinically significant acute infection and/or systemic antibiotic use within 3 days.*
- Perform Rapid Diagnostic Test for malaria. In case of a positive result, vaccination should be postponed until at least five days after completing treatment as per national guidelines.
- Perform Step 2 Randomization. (Unblinded staff)
- Collect blood sample (approximately 5 mL) for serology testing prior to vaccination.
- Administer blinded meningococcal vaccine, according to randomization assignment. The preparation and administration of study meningococcal vaccine will be performed by unblinded staff.
- After vaccination, the subject will be observed for at least 30 minutes for any immediate post-vaccination reactions, with appropriate medical treatment readily available in case of a rare anaphylactic reaction following the administration of vaccines. Solicited local and systemic AEs, any unsolicited AEs, vital signs and axillary body temperature will be recorded. All safety data collected within 30 minutes post-vaccination should be recorded in the subject's source documents or eCRFs.
- The participant's infant immunization card and medical record will be updated to indicate the receipt of a serogroup A meningococcal vaccine.

- A measles-rubella-containing vaccine will be administered, according to the "enhanced" EPI schedule. *Note: the administered "enhanced" EPI vaccines are also to be recorded on the participant's infant immunization card.*
- Schedule Visit 2 approximately 7 days after vaccination.
- Field workers will visit participant homes each day for the next 4 to 7 days as described in Section 5.4

5.3 Planned Study Visits

5.3.1 Follow-up

Visit #2 (Day 8 + 3 days after study meningococcal vaccination)

Study subjects will return for follow-up evaluation to the clinical study site approximately 7 days following meningococcal vaccination. Alternatively, a home visit may be performed by a medically qualified site personnel. At this visit, investigator or delegate will perform the following:

- Review of solicited and unsolicited AEs experienced during the initial 4 days after vaccination, assisted by review of home visit worksheets which are completed by a daily visit by field workers during the first 4 days following vaccination
- Assessment of any ongoing solicited AEs on Day 8 post-vaccination (note that all ongoing solicited AEs beyond Day 8 must be followed up daily by site staff until resolution)
- Medical interview of subject's parents/guardians to assess any unsolicited AEs, SAEs since previous study visit
- Collection of concomitant medications and vaccinations
- Physical examination including assessment of vital signs (heart rate and respiratory rate) and axillary body temperature
- Schedule Visit 3, approximately 28 days after vaccination

Visit #3 (Day 29 + 7 days after study meningococcal vaccination)

Study subjects will return for follow-up evaluation to the clinical study site approximately 28 days following meningococcal vaccination. At this visit, investigator or delegate will perform the following:

- Review of unsolicited AEs experienced during the 28 days after vaccination using home visit worksheets
- Medical interview of subject's parents/guardians to determine if any unsolicited AEs or SAEs occurred and if any concomitant medication or vaccines were received since the last study visit.
- Check any ongoing AEs and concomitant medications since the last study visit and record resolution date (the end date), if available in the source documents or eCRFs.
- Physical examination including assessment of heart rate, respiratory rate, and axillary body temperature

- Collection of blood sample (approximately 10 mL) for serology testing.
- Schedule Visit 4, approximately 6 months after vaccination

Visit #4 (Day 181 ± 14 days after study meningococcal vaccination)
Study subjects will return for follow-up evaluation to the clinical study site approximately 6 months following meningococcal vaccination. At this visit, investigator or delegate will perform the following:

- Medical interview of subject's parents/guardians to determine if any SAEs occurred since the last study visit.
- Physical examination including assessment of heart rate, respiratory rate, and axillary body temperature
- Collection of blood sample (approximately 5 mL) for serology testing.
- For participants randomized and enrolled in the 9-month groups, a measles-rubella containing vaccine will be administered at this 15-month old visit.
- Schedule Visit 5, approximately 2 years after vaccination

5.3.2 Final Study Visit

Visit #5, Final Visit (Day 730 ± 45 days after study meningococcal vaccination)
Study subjects will return for follow-up evaluation to the clinical study site approximately 2 years following meningococcal vaccination. At this visit, investigator or delegate will perform the following:

- Medical interview of subject's parents/guardians to determine if any SAEs occurred since the last study visit.
- Physical examination including assessment of heart rate, respiratory rate, and axillary body temperature
- Collection of blood sample (approximately 5 mL) for serology testing.

5.3.3 Early Termination Visit

A subject may discontinue study participation at any time prior to the last planned study visit. This is referred to as an early termination from the study. The reasons for early termination from the study include: adverse event, death, withdrawal of consent, lost to follow-up, administrative reason, protocol deviation, or other reasons upon the investigator's judgement. The investigator should make every effort to investigate whether or not safety concerns (adverse event, SAE or death) may have been related to the subject's discontinuation from the study. If a safety concern has been associated with the subject's discontinuation, this must be described on the Termination electronic case report form (eCRF) page, even if it is not the primary reason for the subject's discontinuation.

When possible, an early termination clinic visit should be performed so that a PE including assessment of vital signs and axillary temperature, can be performed and the collection of blood (approximately 5 mL) may be possible. Concomitant medications and vaccinations may be collected through Day 29.

5.4 Field Worker Home or Community Visits

In lieu of phone calls, electronic messaging, and postal mail, study team members who are designated as community field workers commonly visit with study participant homes and local villages throughout the study to facilitate the communication of important study information, such as providing reminders for upcoming study visits and to continue to address any questions or concerns regarding the study. During the first 4-days post-vaccination, field workers will interview parent(s)/guardian(s) and complete the memory aid document required for the assessment of daily reactogenicity described in Section 7.1.2. For instances where there is reactogenicity of grade 2 or higher at the fourth day post-vaccination (Day 5), then field workers will continue the daily visits to complete the memory aid document until resolution or the severity of the reactogenicity is grade 1. The active community engagement of the study team members helps to enable trust, enhances study compliance, and decreases the risk of losses to follow-up. Reactogenicity events or other clinical concerns noted by the field workers will be discussed with the study physicians. These field worker visits may lead to unscheduled study visits, upon investigator judgement.

5.5 Unscheduled Study Visits

Unscheduled clinic visits may be conducted for safety concerns, upon investigator judgement. A medical evaluation may determine that the study participant may need escalated care and will be provided appropriate referral, when the need arises.

5.6 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or protocol-specific MOP requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions should be developed by the site and implemented promptly. It is the responsibility of the site Principal Investigator (PI) and other study personnel to use continuous vigilance to identify and report protocol deviations. All individual protocol deviations will be addressed in subject study records. All protocol deviations, either individual, product, or site-specific will be collected and the record stored in a sponsor-determined location. Protocol deviations must be sent to the local IRB/IEC per its guidelines. The site PI and other study personnel are responsible for knowing and adhering to their IRB/IEC requirements.

It is the responsibility of the site PI and personnel to use continuous vigilance to identify and report deviations within five working days of identification of the protocol deviation, or within five working days of the scheduled protocol-required activity. All deviations must be promptly reported to DMID per the Data Coordinating Center (DCC) protocol deviation reporting procedures.

All protocol deviations, as defined above, must be addressed in study subject data collection forms. A completed copy of the DMID Protocol Deviation Form must be maintained in the Regulatory File, as well as in the subject's chart. Protocol deviations must be sent to the local IRB/IEC per their guidelines. The site PI and personnel are responsible for knowing and adhering to their IRB requirements.

6 DESCRIPTION OF CLINICAL AND LABORATORY EVALUATIONS

6.1 Clinical Evaluations

Complete medical history will be obtained by interview of subjects on the day of study vaccination prior to the study vaccination. Subjects will be queried regarding a history of significant medical disorders of the head, eyes, ears, nose, throat, mouth, cardiovascular system, lungs, gastrointestinal tract, liver, pancreas, kidney, urologic system, nervous system, blood, lymph nodes, endocrine system, musculoskeletal system, skin, and genital/reproductive tract. A history of any allergies, cancer, immunodeficiency, and autoimmune disease will be solicited. At follow-up visits after the study vaccination, an interim medical history will be obtained by interview of subjects noting any changes since the previous clinic visit or contact. All concomitant medications and an updated vaccination history will also be collected through Day 29.

At the Day 1 visit prior to the study vaccination, a physical examination will be performed on all subjects to include the following organs and organ systems: including skin, head and neck, lungs, heart, liver, spleen, extremities, lymph nodes, and nervous system, by a study clinician (site principal investigator or sub-investigator). At follow-up visits after the first study vaccination, a targeted physical examination may be performed, if indicated based on the subject's interim medical history, by a study licensed clinician as the site principal investigator or sub-investigator. Targeted physical examinations should also include an assessment for any adverse events.

Vital signs (heart rate and respiratory rate) and axillary body temperature will be collected prior to study vaccination and at follow-up visits.

Height and weight will be collected at the Day 1 visit prior to the first study vaccination for the assessment of nutritional status age Z-score (HAZ/LAZ).

Subjects will be observed in the clinic for at least 30 minutes after receiving the study meningitis vaccination. The study vaccination site will be examined, post-administration reactogenicity assessments will be performed, and any AE/SAEs will be recorded on the appropriate data collection form prior to discharge from the clinic.

Reactogenicity assessments will include an assessment of solicited AEs occurring from the time of each study meningitis vaccination through Day 8 after study vaccination with a meningococcal vaccine, which includes an assessment of meningitis vaccine injection site reactions including erythema (redness), swelling, and pain, as well as systemic reactions including fever, feverishness, irritability, decrease eating, vomiting, and drowsiness. Pre-administration reactogenicity assessments will be performed prior to each study meningitis vaccination to establish baseline, then the study vaccination will be given.

Parents/guardians, with the help of study field workers, will complete a subject memory aid from the time of study vaccination through at least 4 days. Subject memory aids will be reviewed by study staff for AEs (solicited injection site and systemic reactions and unsolicited AEs) at the clinic Visit 2 (Day 8).

6.2 Laboratory Evaluations

6.2.1 Clinical Laboratory Evaluations

None required.

6.2.2 Research Assays

Venous blood for the measurement of serum-based immune response measures will be performed from collected blood prior to vaccination (Day 1), 4 weeks (Day 29), 6 months (Day 181), and 2 years (Day 730) after vaccination. Subjects who withdraw early or are lost to follow-up will have their immune response measures on available sera. The assays to measure the immune responses to vaccination will be performed at the following indicated specialized laboratories:

- Assays for meningococcal serogroup-specific rSBA will be performed at UKHSA (Manchester, UK).
- Enzyme-Linked Immunosorbent Assays (ELISAs) for anti-Measles and anti-Rubella IgG antibody will be performed at VisMederi (Siena, Italy).
- Yellow Fever plaque reduction neutralization test (PRNT) will be performed at VisMederi (Siena, Italy).

Due to sensitivity regarding blood volumes drawn from young children, we calculated the approximate serum volumes required for each assay (including backup sample volumes) and the timing of the blood draws, to provide justification for the blood collection. This information is available in the MOP.

Individual study results will not be reported to parent or placed in medical record.

6.2.2.1 Laboratory Specimen Preparation, Handling, and Storage

The blood will be processed and aliquoted according to the Manual of Procedures. All serum aliquots will be stored at a temperature of -20°C or below.

6.2.2.2 Laboratory Specimen Shipping

Samples for immunogenicity testing will be packaged according to International Air Transport Association (IATA) regulations and shipped via an international shipping courier to the respective laboratories according to the MOP.

7 ASSESSMENT OF SAFETY

7.1 Assessing and Recording Safety Parameters

7.1.1 Adverse Events (AEs)

Adverse Event (AE): ICH E6 GCP defines an AE as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product. The occurrence of an AE may come to the attention of study staff members during study visits (including field visits) and interviews of a study recipient presenting for medical care, or upon review by a study monitor.

AEs, including solicited injection site and systemic (subjective and quantitative) reactions, not meeting the protocol-defined criteria for SAEs, will be recorded on the appropriate data collection form (DCF) or entered into the eCRF. Information to be collected for unsolicited non-serious AEs includes event description, date of onset, licensed study physician's assessment of severity and relationship to study product or alternate etiology (if not related to study product), date of resolution, seriousness, and outcome. AEs occurring during the trial-collection and reporting period will be documented appropriately regardless of relationship to study product. AEs will be followed through resolution.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the severity of any pre-existing medical condition increases, it will be recorded as an AE. The time of reference for the AE is to be the time from receipt of the randomized blinded meningococcal vaccine.

7.1.1.1 Adverse Events Grading

All AEs (laboratory and clinical symptoms) will be graded for severity and assessed for relationship to study product (see definitions). AEs characterized as intermittent require documentation of onset and duration of each episode. The start and resolution date of each reported AE will be recorded on the appropriate data collection form and eCRF. Increases in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of intensity. Whereas, only the resolution date and not each decrease in severity is required to be documented.

Severity of Event:

AEs will be assessed by the investigator using a protocol-defined grading system (Appendix B). For events not included in the protocol-defined grading system, the following guidelines will be used to quantify severity:

- Mild (Grade 1): Events that are usually transient and may require only minimal or no treatment or therapeutic intervention and generally do not interfere with the subject's usual activities of daily living.
- Moderate (Grade 2): Events that are usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe (Grade 3): Events interrupt usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. Severe events are usually incapacitating.
- Potentially Life-Threatening (Grade 4): Events that are potentially life-threatening and require hospitalization.
- Death (Grade 5): Events resulting in death (*Note: this grade is not specifically listed in the grading tables*)

Relationship to Study Product: The assessment of the AE's relationship to study product will be done by the licensed study physician and the assessment will be part of the documentation process. Whether the AE is related or not, is not a factor in determining what is or is not reported in this trial. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. In a clinical trial, the study product must always be suspect. The relationship to study product will be assessed for AEs using the terms related or not related:

- Related – There is a reasonable possibility that the study product caused the AE. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the AE.
- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

7.1.2 Reactogenicity

Reactogenicity events are AEs that are common and known to occur following administration of this type of study vaccine. The following Toxicity Grading Scales will be used to grade solicited local (meningitis vaccine injection site) and systemic (subjective and quantitative) reactions:

Reactogenicity events are AEs that are common and known to occur following administration of this type of study vaccine. The following are the local and systemic solicited AE which are to be collected during the study.

Solicited local reactions: pain/tenderness, swelling/induration, and erythema/redness

Solicited systemic reactions: irritability, drowsiness/lethargy, decrease eating/anorexia, vomiting, fever, and feverish

Table 6. Toxicity Grading Scale – Solicited Local Reactions

Local (Administration Site) Reaction	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Pain/tenderness	Causes no or minimal limitation of use of limb	Causes greater than minimal limitation of use of limb	Inability to perform usual social & functional activities with the limb	Inability to perform basic self-care function OR hospitalization indicated
Swelling/induration	≤2.5 cm in diameter	>2.5 cm in diameter	Presence of ulceration OR secondary infection OR phlebitis OR sterile abscess OR drainage	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Erythema/Redness	≤2.5 cm in diameter	>2.5cm up to 5 cm	>5 cm	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)

Table 7. Subjective Solicited Systemic Reactogenicity Grading

Systemic (Subjective)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Irritability Drowsiness/ Lethargy Decrease Eating/Anorexia	Causes no or minimal interference with usual social & functional activities with no intervention indicated	Causes greater than minimal interference with usual social & functional activities with intervention indicated	Causes inability to perform usual social & functional activities with intervention or hospitalization indicated	Inability to perform basic self-care function AND hospitalization indicated
Vomiting	Transient or intermittent AND no or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Fever (Axillary)	38.0 to <38.6°C	≥38.6 to <39.3°C	≥39.3°C to <40.0°C	≥40.0°C
Feverish	Events that are usually transient and maybe require only minimal or no treatment or therapeutic	Events that are usually alleviated with additional specific therapeutic intervention. The event interferes with	Events interrupt usual activities of daily living, or significantly affects clinical status, or may require	Events that are potentially life-threatening and require hospitalization.

	intervention and generally do not interfere with the subject's usual activities of daily living	usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.	intensive therapeutic intervention. Severe events are usually incapacitating.	

7.1.3 Serious Adverse Events (SAEs)

Serious Adverse Event (SAE): An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the site principal investigator or sponsor, it results in any of the following outcomes:

1. Death.
2. Is life-threatening (i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically might have caused death if it were more severe.
3. Required or prolonged hospitalization.
4. Persistent or significant disability or incapacity (i.e., the event causes a substantial disruption of a person's ability to conduct normal life functions).
5. Congenital anomaly/birth defect.
6. An important and significant medical event that may not be immediately life threatening or resulting in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes listed above.

AEs which do not fall into these categories are defined as non-serious AEs. It should be noted that a severe AE need not be serious in nature and that a SAE need not, by definition, be severe.

7.2 Specification of Safety Parameters

Safety will be assessed by the frequency and severity of solicited local and systemic adverse reactions within 7 days of blinded study meningococcal vaccine; unsolicited adverse events within 28 days of blinded study meningococcal vaccine; and serious adverse events during the entire study period (i.e., enrollment through last visit).

7.2.1 Unsolicited Events

Unsolicited events are any other AEs that occur following administration of study product.

7.2.2 Medically-Attended Adverse Events (MAAEs)

Not applicable.

7.3 Reporting Procedures

Solicited injection site and systemic reactogenicity events will be documented and reported from the time of study vaccination through 7 days after study meningococcal vaccination. *Note that community field workers will only perform the daily visits to complete the documentation of axillary body temperature, size of swelling/induration, and other reactogenicity during the initial 4 days following vaccination. The remaining days prior to Visit 2 may not be documented if the events are grade 1 or resolved, especially from illiterate families, and this will not be considered a protocol deviation. For instances where there is reactogenicity of grade 2 or higher at the fourth day post-vaccination (Day 5), then field workers will continue the daily visits to complete the memory aid document until resolution or the severity of the reactogenicity is grade 1*. However, through interviewing the parent/guardian, reactogenicity events through 7 days after study meningococcal vaccination are intended to be collected. Unsolicited non-serious AEs will be documented and reported from the time of study meningococcal vaccination through 28 days after study meningococcal vaccination. SAEs will be documented and reported from the time of enrollment through approximately 2 years after study meningococcal vaccination.

7.3.1 Reporting Serious Adverse Events

SAEs will be:

- Captured both on the SAE form as well as on the AE eCRF.
- Will be reported within 24 hours of the site becoming aware of the event to the DMID Pharmacovigilance Group noted in this section.
- Will be reported by the investigator to their corresponding EC/IRB or applicable regulatory authorities in accordance with institutional policy/regulatory requirements and adequate documentation of this notification must be recorded in the regulatory file.

The SAE form should be completed as thoroughly as possible with all available details of the event. Even if the investigator does not have all information regarding an SAE, the SAE should still be submitted within 24 hours. Once additional relevant information is received, the SAE form should be updated within 24 hours. The investigator will always provide an assessment of causality at the time of the initial report.

The Sponsor and its designee must also comply with the applicable regulatory requirement(s) related to the reporting of Suspected Unexpected Serious Adverse Reactions (also referred to as "SUSARs") to the regulatory authority(ies) and the IRB/EC. If a SUSAR or other safety signal relating to use of one of the study vaccines is reported to the sponsor or its designee, the sponsor will communicate the information to the investigator and the investigator will be responsible for submitting this information to the EC/IRB and other relevant authorities.

SAEs will be followed until resolution even if this extends beyond the study-reporting period. Resolution of an AE is defined as the return to pretreatment status or stabilization of the condition with the expectation that it will remain chronic.

Any AE that meets a protocol-defined serious criterion must be submitted immediately (within 24 hours of site awareness) on an SAE form to the DMID Pharmacovigilance Group, at the following address:

DMID Pharmacovigilance Group
Clinical Research Operations and Management Support (CROMS)
6500 Rock Spring Dr. Suite 650
Bethesda, MD 20817, USA
SAE Hot Line: 1-800-537-9979 (US) or 1-301-897-1709 (outside US)
SAE FAX Number: 1-800-275-7619 (US) or 1-301-897-1710 (outside US)
SAE Email Address: PVG@dmidcroms.com

In addition to the SAE form, select SAE data fields must also be entered into the DCC system. Please see the protocol-specific MOP for details regarding this procedure.

Other supporting documentation of the event may be requested by the DMID Pharmacovigilance Group and should be provided as soon as possible.

The site will send a copy of the SAE report(s) to the Independent Safety Monitor (ISM) (as deemed necessary) when they are provided to the DMID Pharmacovigilance Group. The DMID Medical Monitor (MM) and DMID Clinical Project Manager will be notified of the SAE by the DMID Pharmacovigilance Group. The DMID MM will review and assess the SAE for regulatory reporting and potential impact on study subject safety and protocol conduct.

At any time after completion of the study, if the site principal investigator (PI) or appropriate sub-investigator becomes aware of an SAE that is suspected to be related to study product, the site PI or appropriate sub-investigator will report the event to the DMID Pharmacovigilance Group.

7.3.2 Regulatory Reporting for Studies Not Conducted Under DMID-Sponsored IND

Following notification from the investigator, the Sponsor will report events that are both serious and unexpected that are related to study product(s) to the Indian and Malian Regulatory Authority within the required timelines as specified in the local guidelines.

7.3.3 Reporting of Pregnancy

Not applicable.

7.4 Type and Duration of Follow-up of Subjects after Adverse Events

AEs will be assessed and followed from initial recognition of the AE through end of the protocol defined follow-up period. SAEs will be followed up through resolution even if duration of follow-up goes beyond the protocol-defined follow-up period. Resolution of an AE is defined as the return to pre-treatment status or stabilization of the condition with the expectation that it will remain chronic.

7.5 Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings

- Not applicable to this protocol.

7.6 Halting Rules

7.6.1 Study Halting Criteria

Additional enrollment and study interventions/administration of study products in this trial will be halted for Data and Safety Monitoring Board (DSMB) review/recommendation if any of the following are reported:

- Any subject experiences ulceration, abscess or necrosis at the injection site that is considered related to study product administration.
- One or more subjects experience laryngospasm, bronchospasm or anaphylaxis within 1 day after administration of study product that is considered related to study product.
- Any subject experiences any Grade 4 AE or an SAE after administration of study product that is considered related to study product.
- 5% or more of subjects (with a minimum of 3 subjects) who received a dose of study vaccine experience the same severe (Grade 3) study vaccine-related injection site reaction, within 7 days of vaccination. Induration (hardness)/edema (swelling) will be measured in mm, but size will not be used as halting criteria.
- 5% or more of subjects (with a minimum of 3 subjects) who received a dose of study vaccine experience the same severe (Grade 3) study vaccine-related subjective systemic reaction, within 7 days of vaccination, for which the severity (grade) is corroborated by study personnel.

If any of the halting rules are met, then the trial will not continue with the remaining enrollments without a review by and recommendation from the DSMB to proceed.

7.7 Safety Oversight

7.7.1 Independent Safety Monitor (ISM)

An ISM is a physician with relevant expertise whose primary responsibility is to provide independent safety monitoring in a timely fashion. Participation is for the duration of the study and the ISM must meet the conflict-of-interest requirements of DMID.

The ISM:

- Will have experience in pediatrics.
- Is in close proximity to the study site and has the authority and ability to readily access subject records in real time.
- May be a member of the participating institution’s staff but preferably be from a different organizational group within the institution.

- Should not be in a direct supervisory relationship with the investigator.
- Should have no direct involvement in the conduct of the study.

The ISM will:

- Sign a Conflict of Interest (COI) certification at the time they are asked to participate and provide updates to this information as needed.
- Receive reports of SAEs deemed related to the study from the site investigator and will be notified by email when DMID is notified of the SAE.
- Evaluate the SAE and report their clinical assessment to DMID, PI and Site Investigator.
- Communicate with the investigator at the participating site as needed.
- Review additional safety related events at the request of DMID.
- Provide additional information to DMID and/or the DSMB by teleconference as requested.

7.7.2 Data and Safety Monitoring Board (DSMB)

Safety oversight will be conducted by a DSMB that is an independent group with expertise to interpret data from this study and will monitor subject safety and advise DMID. The DSMB members will be separate and independent of study personnel participating in this study and should not have scientific, financial or other conflict of interest related to this study. DSMBs must consist of at least three voting members, including a biostatistician experienced in statistical methods for clinical trials and a clinician with relevant expertise.

The DSMB will operate under the rules of a DMID-approved charter that defines the data elements to be assessed and the procedures for data reviews and will be written at the organizational meeting of the DSMB. Procedures for DSMB reviews/meetings will be defined in the charter. Reports may include enrollment and demographic information, medical history, concomitant medications, physical assessments, clinical laboratory values, dosing compliance, and solicited and unsolicited AE/SAEs. The DSMB will review SAEs on a regular basis and ad hoc during this trial. The DMID MM and the ISM (as deemed necessary) will be responsible for reviewing SAEs in real time.

As defined in the charter in Section 9.5.1, the DSMB will review data at specified times during the course of the study for subject and overall study progress (at a minimum of annually) and will conduct ad hoc reviews as appropriate when a halting rule is met or for immediate concerns regarding observations during this study. A final review meeting will also be held 6 to 8 months after clinical database lock to review the cumulative unblinded safety and efficacy data for the study.

Additional data may be requested by the DSMB, and interim statistical reports may be generated as deemed necessary and appropriate by DMID. The DSMB may receive data in aggregate and presented by treatment arm. The DSMB may also be provided with expected and observed rates of the expected AEs in an unblinded fashion and may request the treatment assignment be unblinded for an individual subject if required for safety assessment. The DSMB will review

grouped and unblinded data in the closed session only. As an outcome of each review/meeting, the DSMB will make a recommendation as to the advisability of proceeding with study vaccinations (as applicable), and to continue, modify, or terminate this trial.

7.7.3 Internal Safety Reviews

A biweekly internal safety review will be conducted throughout the enrollment period of the study. From completion of enrollment through the follow-up period, the regularity of these internal safety reviews may be less frequent. The internal safety review members will consist of the protocol chair, Vaccine and Treatment Evaluation Unit (VTEU) principal investigator, site principal investigators, the DMID MO and MM. The information to be reviewed will consist of the enrollment and visit compliance of study participants, AE reports, and reactogenicity. These reports (in aggregate or listings) will be presented as blinded and uncleaned data from weekly and monthly safety reports generated from SCHARP. SCHARP weekly reports are scheduled to be posted every Thursday and monthly reports on the first Thursday of each month. Whereupon any safety concerns are potentially detected, the issue may be directed to the DSMB's awareness for discussion. A temporary halt may be declared, upon investigator's judgement.

8 HUMAN SUBJECTS PROTECTION

8.1 Institutional Review Board/Independent Ethics Committee

This study will be conducted in accordance with the ethical principles set out in the World Medical Association Declaration of Helsinki, The Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Biomedical Research Involving Human Subjects, and in conformity with ICH GCP and with local Mali applicable regulations.

This study will be conducted under the auspices of the following Institutional Review Boards (IRBs)/ Ethics Committees (ECs):

- Research Ethics Committee of the Faculté de Médecine, de et d'Odonto-Stomatologie – Faculté de Pharmacie (FMOS-FAPH), Bamako, Mali (DHHS OHRP Federal Wide Assurance number 00009970)
- University of Maryland, Baltimore Institutional Review Board (UMB IRB), Baltimore, Maryland, U.S.A. (DHHS OHRP Federal Wide Assurance number 00007145)

The principal investigator will obtain EC/IRB approvals for this protocol and send supporting documentation to the DMID before initiating recruitment of subjects. The IRB/IEC must be registered with OHRP as applicable to the research. DMID must receive the documentation that verifies IRB/IEC-approval for this protocol, associated informed consent documents, and upon request any recruitment material and handouts or surveys intended for the subjects, prior to the recruitment and enrollment of subjects. Any amendments to the protocol or consent materials will be approved by the IRB/IEC before they are implemented. IRB/IEC review and approval will occur at least annually throughout the enrollment and follow-up of subjects and may cease if annual review is no longer required by applicable regulations and the IRB/IEC. The investigator will notify the IRB/IEC of deviations from the protocol and reportable SAEs, as applicable to the IRB/IEC policy.

The IRB/IEC will determine that adequate provisions are made for soliciting the permission of each child's parent(s) or legal guardian, including whether permission of one parent is sufficient for research or whether permission is to be obtained from both parents.

8.2 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate (or agreeing that their child can participate) in the study and continues throughout the subject's participation in the study. Before any study-related activities and in agreement with ICH-GCP and the applicable local ethical and regulatory requirements, the site investigator must ensure that the subject (or subject's parent/guardian) is fully informed about the objectives, procedures, potential risks, and potential benefits of study participation.

During the informed consent process, a suitably delegated member of the clinical trial team will review the content of the ICF line by line with the subject's parent/guardian. If the subject or

subject's parent/guardian is literate (French in Mali), this review will take place in French. If the subject's parent/guardian is not sufficiently literate (French in Mali) to read and understand the ICF, the content of the same document will be translated in writing and recorded line by line in the local national Malian language, Bambara. This translation and recording will be performed by only Government national language translation office in country. The process must be witnessed by an impartial witness who is fluent in both French and in Bambara and who will subsequently be required to sign to attest that the information in the ICF has been provided accurately and in full to the participant. As local languages are spoken but not written, attempts to translate the French ICF into ICFs written in the local languages has proved unsuccessful (when subjected to back-translation); hence the process for verbal translation has been developed and approved by the local EC. In all cases, the subject or subject's parent/guardian will be encouraged to ask questions about the study and must have the questions answered and be given sufficient time to decide if they would like to participate (or would like their child to participate) in the study. It will be emphasized that participation is voluntary, and that the subject has the right to discontinue (or to have their child discontinue) from the study at any time without giving any reason and without compromising their other rights in any way. The site investigator or their designee must obtain the subject's (or subject's parent/guardian's) voluntary, signed or fingerprinted or personally marked, and dated ICF (also signed by the impartial witness if applicable), before any study-related procedures are performed. Study staff must document the informed consent process in the source document. The ICF will be completed and signed in two originals (or in one original with certified copy), of which one original will be kept in the site study file, and one original or certified copy will be given to the subject (or subject's parent/guardian) for their records.

8.3 Consent for Future Use of Stored Specimens and Data

Residual samples/specimens are those that are left over after protocol-specified testing and this study has been completed. Subjects will be asked for permission to keep any remaining (residual) specimens (serum) derived from venous blood samples for possible use in future research studies, such as examining additional immunological assessments or testing for antibodies against other vaccines, viruses or bacteria. These residual specimens will be stored coded indefinitely at the CVD (Baltimore, MD). Specimens may be shared with DMID, SIIPL, PATH, UKHSA, or VisMederi. Future-use stored specimens which have been coded may be shared with other investigators in the future. The recipients of specimens will be informed that these specimens have a NIH certificate of confidentiality. The information provided to a recipient will not contain direct identifiable information.

8.4 Subject Confidentiality

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality includes documentation, investigation data, subject's clinical information, and all other information generated during participation in the study. No information concerning the study, or the data generated from the study will be released

to any unauthorized third party without prior written approval of the DMID and the subject. Subject confidentiality will be maintained when study results are published or discussed in conferences. The study monitor or other authorized representatives of the sponsor or governmental regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

All records will be kept locked, and all computer entry and networking programs will be carried out with coded numbers only and with password protected systems. All non-clinical specimens, evaluation forms, reports, and other records that leave the site will be identified only by a coded number.

8.5 Costs, Subject Compensation, and Research Related Injuries

Subjects (or their parent/guardian) in Mali will be compensated for their time in this study and be reimbursed for travel to attend study visits. These will be explained in the ICF. Study subjects (or their parent/guardian) will not be charged for study immunizations, research clinic visits, research-related examinations, or research-related laboratory tests. As part of the assessment and management of AEs, all medical care required by the subjects according to good national medical practice will be provided by the study team for the study duration and the subject's parent/guardian will not need to pay for this. Subjects may be compensated for their participation in this trial. Compensation will be in accordance with the local IRB's policies and procedures, and subject to IRB approval.

If it is determined by the site principal investigator that an injury occurred to a subject as a direct result of the tests or treatments that are done for this trial, then referrals to appropriate health care facilities will be provided to the subject. Clinical trial insurance is legally required in Mali. Study personnel will try to reduce, control, and treat any complications from this trial, but chronic care will not be provided. Immediate medical treatment may be provided by the participating site.

9 STATISTICAL CONSIDERATIONS

9.1 Overview and Study Design

This is a Phase 3, randomized, single site, blinded non-inferiority trial to test the safety and immunogenicity of the NmCV-5 vaccine when administered at 9 months of age and when administered at 15 months of age. All participants will be randomly assigned to receive either NmCV-5 or MenACWY-TT, and all participants will be randomly assigned to receive one of these vaccines at either 9 months of age or at 15 months of age, along with scheduled EPI vaccines (Section 2.1).

9.2 Study Hypotheses

The co-primary objectives of the study are to demonstrate non-inferiority of the overall seroprotective response of NmCV-5 as compared to the seroprotective response of MenACWY-TT 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 null hypothesis that the seroprotective response elicited by NmCV-5 to at least one of the meningococcal serotypes A, C, W, X or Y is inferior to the seroprotective response elicited by MenACWY-TT in favor of the alternative hypothesis that the seroprotective response to all five meningococcal serogroups elicited after one dose of NmCV-5 are non-inferior to those elicited by one dose of MenACWY-TT. For each vaccination age group and for each of the serogroups A, C, Y and W, the corresponding hypothesis test will be based on the difference in the proportion of participants randomized to receive NmCV-5 who show seroprotective response to the specific serogroup, relative to the proportion of participants randomized to receive MenACWY-TT who show seroprotective response to the same serogroup. For serogroup X, the hypothesis test will be based on the difference in the proportion of participants randomized to receive NmCV-5 who show seroprotective response to the serogroup X relative to the proportion of participants randomized to receive MenACWY-TT showing seroprotective response to the serogroup with the lowest proportion of seroprotective response in that arm. For each meningococcal serogroup, vaccine seroprotective response will be based on a rabbit serum bactericidal antibody (rSBA) assay and the primary immunological endpoint is defined as post-vaccination rSBA titers ≥ 8 at Day 29. Within each age group, non-inferiority of the vaccine for each serogroup will be declared if the lower bound of the two-sided 95% confidence intervals for the difference in proportions of participants with seroprotective response is above -10% (-0.1). 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 seroprotective response, as defined above, is achieved for all five serogroups.

Consistent with the secondary safety endpoint to assess the safety and tolerability of a single dose of NmCV-5, a descriptive analysis approach will be used, with no statistical tests of hypothesis. These analyses are described in Section 9.6.

A secondary immunogenicity objective is to demonstrate the superiority of the NmCV-5 vaccine to elicit seroprotective response to the meningococcal serogroup X. To achieve this objective, the study will test a null hypothesis of the difference in the proportion of participants with vaccine seroprotective response to serogroup X equal or less than 30% (0.3) versus an alternative hypothesis of the difference in proportions of 30% or greater. Vaccine seroprotective response to serogroup X has been defined above, with non-inferiority declared if the lower bound of the two-sided 95% confidence interval for the difference in proportion of participants with seroprotective response is at or above 10%.

The secondary objective related to the immunogenicity of EPI vaccines is to demonstrate that seroprotective response elicited by EPI vaccines when co-administered with NmCV-5 is non-inferior to the seroprotective response elicited by these same vaccines when co-administered with MenACWY-TT. The study will test the null hypothesis that, for each EPI vaccine, the difference in the proportion of participants showing seroprotective response (in the NmCV-5 arm relative to the MenACWY-TT arm) is equal or less than 10% (-0.1) in favor of the alternative hypothesis that the difference is greater than -10% (0.1). The seroprotective response to measles vaccination is defined as anti-measles IgG concentration > 90 mIU/mL, the seroprotective response to yellow fever vaccine is defined as neutralizing antibody titers ≥ 1:8, and the seroprotective response to rubella vaccine is to be according to the manufacturer's specified cutoff, for a commercially-available and validated rubella IgG assay, all from samples collected at Day 29 visit. For each EPI vaccine, non-inferiority will be declared if the lower bound of a two-sided 95% confidence interval of the difference in proportion of participants with seroprotective response is above -10% (-0.1).

9.3 Sample Size Considerations

Table 8 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. 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.

Finally, calculation of Power in Table 8 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.

Table 8. 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 Sero-response in MenACWY-TT arm	Difference in proportion of sero-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%

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 9 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 9. 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 Sero-response among Serogroups A, C, W,	Difference in sero-response (Serogroup X in NmCV-5 - lowest proportion among Serogroups A, C, W, Y in MenACWY-TT)	Power

	Y in MenACWY-TT arm	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.

9.4 Treatment Assignment Procedures

9.4.1 Randomization Procedures

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 MenACWY-TT, 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.

9.4.2 Masking Procedures

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 Treatment Unblinding Procedure document. There are no circumstances under which it is expected that unblinding will be necessary for provision of medical treatment or to otherwise protect the safety of study participants. If the site investigator or designee feels that specific product knowledge is necessary to protect participant safety, the site investigator or designee will notify the PC and DMID according to procedures described in the MOP. In the event of a serious adverse event requiring submission to regulatory authorities, unblinding information for the specific participant will be provided by SCHARP as required.

9.5 Planned Interim Analyses

9.5.1 Interim Safety Review

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 MM and the ISM (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.

Procedures for DSMB reviews/meetings will be defined in the charter. Reports may include enrollment and demographic information, medical history, concomitant medications, physical assessments, clinical laboratory values, dosing compliance, and solicited and unsolicited AE/SAEs. 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.

We note that statistical analyses of secondary safety endpoints (along with other primary and secondary immunogenicity endpoints) will be conducted before the end of the study, as detailed in Section 9.6.

9.5.2 Interim Immunogenicity or Efficacy Review

No formal interim analyses (i.e. formal test of hypothesis) on partially accumulated data (data available in only a fraction of the targeted number of participants) will be conducted. No statistical interim analyses will be conducted, understanding by this the sequential testing of a statistical hypothesis for which adjustment of type I error probability is required.

However, and as per request of the DSMB, basic descriptive statistics related to immunogenicity endpoints may be included, if and when available, in the close portion of the DSMB reports. These may include statistics per vaccination arm, but will not include the estimation of the statistic on which the evaluation of non-inferiority will be based upon (i.e. 95% confidence interval for the difference in the proportion of participants with seroprotective response). Thus, no formal interim testing of the primary or secondary immunogenicity endpoints are planned, and no adjustment on the type I error rate will be conducted.

We note that statistical analyses of primary and secondary immunogenicity endpoints (along with secondary safety endpoints) will be conducted before the end of the study, as detailed in Section 9.6.

9.6 Analysis Plan

This section describes the statistical analyses for the primary and secondary endpoints. Analysis of tertiary and exploratory endpoints will be described in the Statistical Analysis Plan.

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. Unblinded results (through grouped analysis) from these statistical analyses will be summarized in at least two study reports (one per age group), which will be submitted to WHO, as these data are critical for timely WHO-PQ review process.

The analyses described above may also be available for presentation and publication to inform the scientific community. Publication of manuscripts may occur at the discretion of the sponsor in accordance with DMID's Expanded Distribution of Clinical Research Endpoint Data Policy.

The Clinical Study Report (CSR) will be completed when all primary and secondary safety, clinical, and immunological endpoint data, cumulated up to the end of the study, are available.

Any available data from the exploratory endpoints may also be included. Additional exploratory endpoint data may be included in an addendum to the CSR, publication of manuscript(s), or other report.

The Safety Analysis Set will include all participants who received the NmCV-5 or MenACWY-TT vaccine at the randomly assigned vaccination age. All safety data from participants in the Safety Analysis Set will be analyzed according to the vaccine group to which the participant was randomized. In the rare instance that a participant receives the wrong intervention vaccine, the Statistical Analysis Plan (SAP) will address how to analyze the participant's safety data.

The Immunogenicity Analysis Set will include all participants who receive the expected meningococcal vaccine, within the randomly assigned age and for whom post-vaccine immunogenicity data is available at least at one timepoint post-vaccination. Analyses of primary and secondary immunogenicity endpoints will be conducted in the Immunogenicity Analysis Set.

Before the final analysis, protocol deviations may be reviewed to determine which protocol deviations could affect the analysis. The per protocol (PP) analysis set will then be defined. Additional analyses of immunogenicity data may be conducted on the PP analysis set. Some or all of the following exclusions may apply: (i) data from all available visits for subjects found to be ineligible at baseline, (ii) data from all visits subsequent to the protocol deviations that are considered to affect the science (iii) data from any visit that occurs substantially out of window.

Analyses of primary endpoints will be performed using SAS v9.4.

No formal multiple comparison adjustments will be employed for multiple primary or secondary endpoints. Unless otherwise noted, 95% confidence intervals (CIs) will be calculated. Statistical tests of non-inferiority and superiority will be 1-sided.

A SAP will be developed by the IDCRC Statistical and Data Science Unit (SDSU) and SCHARP and finalized prior to data lock, and prior to the main analysis of the primary and secondary endpoints. Unless specified otherwise in the SAP, missing data will not be imputed.

General Approach

Unless otherwise noted in the SAP, continuous variables will be summarized using the following descriptive statistics: mean, standard deviation, median, quartiles (25^{th} and 75^{th} percentiles), maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. Unless otherwise specified in the SAP, geometric means of relevant continuous endpoints will be computed as Williams means.

Analysis of the Co-Primary Immunogenicity Endpoint(s)

Analysis of the co-primary immunogenicity endpoints will be conducted for the Immunogenicity Analysis Set. In each arm, the proportion of participants with vaccine seroprotective response, defined as post-vaccination rSBA titers ≥ 8 at Day 29, will be calculated for all serogroups. The

difference in proportions will be estimated and 95% CI will be calculated using the Miettinen-Nurminen method.

For serogroup X, the test for non-inferiority will be based on the different in the proportion of participants with seroprotective response to serogroup X among those randomized to NmCV-5 and the proportion of participants with seroprotective response to the serogroup with the lowest seroprotective response rate among those randomized to MenACWY-TT.

Analysis of the Secondary Immunogenicity Endpoint(s)

The superiority of seroprotective response to serogroup X among those randomized to NmCV-5 relative to those randomized to MenACWY-TT will be based on the difference in proportions of participants with seroprotective response to serogroup X and its 95% CI, as estimated using the Miettinen-Nurminen method.

The non-inferiority of seroprotective response to EPI vaccines administered concurrently with the NmCV-5 or MenACWY-TT meningococcal vaccines will be based on the difference in the proportion of participants with seroprotective response to each of these vaccines, between vaccination arms. The difference of proportions and the corresponding 95% CI will be calculated using the Miettinen-Nurminen method.

Finally, to better understand and illustrate the immunological response elicited by the NmCV-5 and MenACWY-TT vaccines, further descriptive analyses will be conducted by vaccination arms for each of the vaccination schedules. These include estimating the proportion of participants (along with 95% confidence intervals) with rSBA titers above 32 and above 128 at their Day 29 visit, as well as the proportion of participants with a 4-fold increase from baseline to their Day 29 visit. Geometric Mean Titers (GMT), with 95% CIs, will also be reported. Similar descriptive analyses will be done at other timepoints (at Day 181 and Day 730 visits), to explore the duration of the immunological response.

Analysis of the Safety Secondary Endpoint(s)

Analysis of the secondary safety endpoint, as well as descriptive analyses of safety data (solicited signs and symptoms and AEs) will be presented for the Safety Analysis Population.

Solicited reactogenicity signs and symptoms (local and systemic) will be summarized by severity for each day post vaccination (Days 1-8) and as the maximum severity over all 7 days. The number and proportion of participants reporting each of the solicited reactogenicity signs and symptoms will be reported, along with 95% confidence intervals, as well as the number and proportion of participants reporting (i) any solicited reactogenicity sign or symptom, (ii) any solicited local reactogenicity sign or symptom and (iii) any solicited systemic reactogenicity sign or symptom.

Unsolicited non-serious AEs will be collected from the time of first vaccination through 28 days after each vaccination. Unsolicited AEs will be coded by the Medical Dictionary for Regulatory

Activities (MedDRA) for preferred term and system organ class SOC. All SAEs will be collected from the time of first vaccination through the end of the study. SAEs will be described by detailed listings showing the event description, MedDRA preferred term and SOC, relevant dates (vaccinations and AEs), severity, relatedness, and outcome for each event. Non-serious unsolicited AEs will be summarized as number and percentage of subjects reporting at least one event in each MedDRA preferred term and SOC, cross tabulated by severity and relationship to study product. Additionally, the proportion of subjects and exact 95% CIs of AEs in aggregate and by MedDRA categories will be computed.

Clinical laboratory data will be summarized as change from baseline and by severity for each visit, and as the maximum over all post study vaccination visits.

Baseline Descriptive Statistics

Summaries of demographic variables such as age at vaccination and sex, will be presented by arm. Summaries of clinical variables, such as weight, length and WHO standardized z-scores of length-for-age, weight-for-age and weight-for-length, at time of vaccination will also be presented by arm.

Tabulation of Individual Subject Data

In general, all data will be listed, sorted by arm and subject, and when appropriate by visit number within subject.

10 ELECTRONIC CASE REPORT FORMS, SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA

The participating site will maintain appropriate medical and research records in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Source data are all information in original records (and certified copies of original records) of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH GCP, regulatory, and institutional requirements.

The study uses direct data entry into an eCRF as source documents by research staff, as well as entering data into the eCRF from source documentation on data collection forms or other types of source documents. The eCRFs serve as the source documents for data collected and entered directly (not recorded elsewhere). The staff will maintain a tracker of eCRFs that serve as the source documents.

A list of all authorized staff as data originators will be included on the Study Personnel/Signature Responsibility List. The staff who will enter source data directly into the eCRF are called “DDE Data Originators”. “Data Entry” staff will enter the data on DCFs into the eCRF.

Paper case report forms derived from the eCRF are provided by the DCC or designee and are to be used when the eCRF is unavailable. Data collected by staff at the homes of subjects will be entered on data collection forms. Details on source data, and instructions for use of the system and completion of the eCRFs are provided in the study MOP.

Each site will permit authorized representatives of the DMID, its designees, and appropriate regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress. These representatives will be permitted access to eCRFs, source data and source documents, which include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects’ memory aid or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Interview of subjects’ parent or legal guardian is sufficient for obtaining medical history.

11 QUALITY CONTROL AND QUALITY ASSURANCE

Following a written DMID-accepted site quality management plan, the site will be responsible for conducting routine quality assurance (QA) and quality control (QC) activities to internally monitor study progress and protocol compliance. The site principal investigator will provide direct access to all study-related sites, eCRFs, source data/data collection forms, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities. The site principal investigator will ensure all study personnel are appropriately trained and applicable documentations are maintained on site.

The DCC will implement quality control procedures beginning with the data entry system and generate data quality control checks that will be run on the database. Any missing data or data anomalies will be communicated to the participating site(s) for clarification and resolution.

12 DATA HANDLING AND RECORD KEEPING

12.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the study staff at the participating site under the supervision of the participating site PI. The site PI is responsible to ensure the accuracy, completeness, and timeliness of the data reported.

The eCRFs and DCF may serve as source documents for data collected. Source documents also include medical records, research charts, or other documents where data is first recorded.

Clinical research data from source documentation or eCRFs, including, but not limited to, AEs/SAEs, concomitant medications, medical history, physical assessments, and clinical laboratory data, will then be collected by the participating site or direct data entered into eCRFs via a 21 CFR Part 11-compliant internet data entry system provided by the DCC, SCHARP. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. AEs and concomitant medications will be coded according to the most current versions of MedDRA and WhoDrug, respectively.

Details on data handling procedures, procedures for data monitoring, and instructions for use of the system and completion of the eCRFs are provided in the study MOP and CRF Completion Guidelines. The MOP will detail which data will be documented onto paper case report forms or when eCRFs will serve as the source documents for data collected. Paper case report forms derived from the eCRF are to be used when the data system or internet is unavailable.

The IDCRC SDSU and SCHARP will be responsible for data management, quality review, analysis, and reporting of the study data.

The IDCRC SDSU, PI and site are responsible for review of data collection tools and processes, and review of data and reports in collaboration with the DMID

The sponsor and/or its designee will provide guidance to the site principal investigators and other study personnel on making corrections to the eCRF.

12.2 Data Coordinating Center/Biostatistician Responsibilities

All eCRFs and source documentation must be reviewed by the clinical team and data entry personnel, who will ensure that they are accurate and complete. AEs must be recorded on the appropriate eCRF, assessed for severity and relationship, and reviewed by the site PI or appropriate sub-investigator.

The data coordinating center for this study will be responsible for data management, quality review, analysis, and reporting of the study data.

At the end of the study, a copy of all datasets, including annotated CRFs and data dictionary, will be provided to DMID.

12.3 Data Capture Methods

Clinical (including, but not limited to, AE/SAEs, concomitant medications, medical history, and physical assessments) and reactogenicity will be collected as described in the Manual of Procedures either on data collection forms by study personnel then entered into the data system or direct data entered into eCRFs via a 21 CFR Part 11-compliant internet data entry system provided by the study data coordinating center. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

The eCRF will be considered a source document when the information is direct data entry (DDE) for source data. The staff who will enter source data directly into the eCRF are called "DDE Data Originators". The PI will list all staff delegated as DDE Data Originators on the Study Personnel/Signature Responsibility List.

12.4 Types of Data

Data for this trial will include clinical, safety, and outcome measures (e.g., reactogenicity, AEs, and immunogenicity data).

12.5 Study Records Retention

Study records and reports including, but not limited to, eCRFs, source documents, ICFs, laboratory test results, and study drug disposition records will be retained for 2 years after a marketing application is approved for the study product for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for the study product, until 3 years after the investigation is discontinued. These documents will be retained for a longer period, however, if required by local regulations. ICFs for future use will be maintained as long as the sample/specimen exists.

No records will be destroyed without the written consent of the sponsor. It is the responsibility of the sponsor to inform the site principal investigator when these documents no longer need to be retained. The participating VTEU sites must contact DMID for authorization prior to the destruction of any study records.

13 CLINICAL MONITORING

Site monitoring is conducted to ensure that the human subjects' protections, study and laboratory procedures, study intervention administration, and data collection processes are of high quality and meet sponsor, ICH/GCP guidelines and applicable regulations, and that this trial is conducted in accordance with the protocol, protocol-specific MOP and applicable sponsor standard operating procedures (SOPs). DMID, the sponsoring agency, or its designee will conduct site-monitoring visits as detailed in the clinical monitoring plan.

Site visits will be made at standard intervals as defined by DMID and may be made more frequently as directed by DMID. Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, eCRFs, informed consent forms, medical and laboratory reports, and protocol and GCP compliance. Site monitors will have access to each participating site, study personnel, and all study documentation according to the DMID-approved site monitoring plan. Study monitors will meet with site principal investigators to discuss any problems and actions to be taken, and will document site visit findings and discussions.

14 PUBLICATION POLICY

Sections 9.5 and 9.6 describe the dissemination of unblinded analysis planned during the study.

Following completion of the study, the lead Principal Investigator is expected to publish the results of this research in a scientific journal. All investigators funded by the NIH must submit or have submitted for them to the National Library of Medicine's PubMed Central (http://www.ncbi.nlm.nih.gov/pmc/) an electronic version of their final, peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication. The NIH Public Access Policy ensures the public has access to the published results of NIH funded research. It requires investigators to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication. Further, the policy stipulates that these papers must be accessible to the public on PubMed Central no later than 12 months after publication.

Refer to:

- NIH Public Access Policy, http://publicaccess.nih.gov/
- NIH Office of Extramural Research (OER) Grants and Funding, http://grants.nih.gov/grants/oer.htm

As of January 2018, all clinical trials supported by the NIH must be registered on ClinicalTrials.gov, no later than 21 days after the enrollment of the first subject. Results of all clinical trials supported by the NIH, generally, need to be submitted no later than 12 months following the primary completion date. A delay of up to 2 years is available for trials that meet certain criteria and have applied for certification of delayed posting.

As part of the result posting a copy of this protocol (and its amendments) and a copy of the Statistical Analysis Plan will be posted on ClinicalTrials.gov.

For this trial the responsible party is DMID which will register the trial and post results.

15 LITERATURE REFERENCES

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16 APPENDICES

Appendix A. Schedule of Events

Group 1: Participant Age (9-month group)	9 mon	9 mon	9 mon	10 mon	15 mon	33 mon	
Visit	**Screen**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**ET**
Study Day		1	8	29	181	730	
Window			+3	+7	±14	±45	
Informed Consent	X						
Demographics[1]	X						
Medical History including review of systems[1]	X						
Determination / Confirmation of Eligibility	X	X					
Rapid Diagnostic Test for malaria		X					
Photo of child		X					
Vital Signs[1,2] including axillary temperature	X		X	X	X	X	(X)
Height, weight[1]	X						
Physical exam[1]	X		X	X	X	X	(X)
Randomization Step 1	X						
Randomization Step 2		X					
Blinded Vaccination		X					
Administration of enhanced EPI vaccines[†]		X			X		
30-minute observation period post meningitis vaccination		X					
7-day Memory Aid (**d**ispense & **c**ollect)[4]		D	C				
AE assessment		X	X	X			(X)
Concomitant medications and vaccinations[1,3]	X	X	X	X			X
SAE assessment		X	X	X	X	X	X
Research Blood Draw (mL)		5 mL		10 mL	5 mL	5 mL	5 mL

Group 2: Participant Age (15-month group)	9 mon	15 mon	15 mon	16 mon	21 mon	39 mon	
Visit	**Screen**	**Visit 1b**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**ET**
Study Day		1	8	29	181	730	
Window			+3	+7	±14	±45	
Informed Consent	X						
Demographics[1]	X						
Medical History including review of systems[1]	X	X					
Determination / Confirmation of Eligibility	X	X					
Rapid Diagnostic Test for malaria		X					
Photo of child		X					
Vital Signs[1,2] including axillary temperature	X	X	X	X	X	X	(X)
Height, weight[1]	X	X					
Physical exam[1]	X	X	X	X	X	X	(X)
Randomization Step 1	X						

Randomization Step 2		X					
Blinded Vaccination		X					
Administration of enhanced EPI vaccines†	X	X					
30-minute observation period post meningitis vaccination		X					
7-day Memory Aid (**d**ispense & **c**ollect) [4]		D	C				
AE assessment		X	X	X			(X)
Concomitant medications and vaccinations[1,3]	X	X	X	X			X
SAE assessment		X	X	X	X	X	X
Research Blood Draw (mL)		5 mL		10 mL	5 mL	5 mL	5 mL

†, Enhanced EPI vaccines at 9-months consist of measles-rubella (MR) and yellow fever (YF) vaccine; the Enhanced EPI vaccine at 15-months consists of MR vaccine.

[1] Conducted after consent obtained

[2] Vital signs include heart rate and respiratory rate.

[3] Concomitant medication and vaccination history will be updated at study visits through Day 29.

[4]Field workers will visit homes as described in Section 5.4.

( ) As applicable

Appendix B. TOXICITY TABLE

The *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1* consists of parameters, or AEs, with severity grading guidance that are to be used in DAIDS clinical trials for safety data reporting to maintain accuracy and consistency in the evaluation of AEs. This study intends to report AEs in alignment with the DAIDS grading guidance. The following table contains the grading of some common reactions and is not intended to be an exhaustive listing. In addition, all deaths related to an AE are to be classified as grade 5.

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Clinical adverse event **NOT** identified elsewhere in the complete grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death
Arrhythmia	No symptoms AND no intervention indicated	No symptoms AND non-urgent intervention indicated	Non-life-threatening symptoms AND non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Hemorrhage	NA	Symptoms AND no transfusion indicated	Symptoms AND Transfusion of ≤ 10 cc/kg of packed RBCs indicated	Life-threatening hypotension OR Transfusion of > 10 cc/kg of packed RBCs indicated
Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated	IV treatment indicated	Life-threatening consequences (e.g., sepsis, tissue necrosis)
Hyper or Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA

Pruritus	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
Rash	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR toxic epidermal necrolysis
Bloating or Distension (of abdomen)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Dysphagia or Odynophagia	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Diarrhea	Liquid stools (more unformed than usual) by usual number of stools	Liquid stools with increased number of stools OR mild dehydration	Liquid stools with moderate dehydration	Life-threatening consequences (e.g., liquid stools resulting in severe dehydration, hypotensive shock)
Mucositis or Stomatitis	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding
Arthralgia	Joint paint causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions

Myalgia (generalized)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Seizures	Seizure lasting < 5minutes with < 24 hours postictal state	Seizure last 5 to < 20 minutes with < 24 hours postictal state	Seizure lasting ≥ 20 minutes OR > 24 hours postictal state	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Syncope	Near syncope without loss of consciousness (e.g., pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NA
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	General urticaria OR Angioedema with intervension indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema