ACYWX-001/ VAC-046

A Phase 1, double blind, randomized, controlled study to evaluate the safety and immunogenicity of a new Meningococcal Conjugate Vaccine containing serogroups A,C,Y,W and X in healthy adults.

Sponsored by:

PATH

Collaborating Partner and Pharmaceutical Support:

Serum Institute of India Private Limited (SIIPL)

Principal Investigator:
Dr. Wilbur H. Chen

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LIST OF ABBREVIATIONS AND ACRONYMS

ABBREVIATION / ACRONYM	DEFINITION
µg or mcg	Microgram
4-PP	4-Pyrrolidinopyridine
AE	adverse event
Alum	Aluminum phosphate
CDC	Centers for Disease Control
CI	Confidence interval
cm	Centimeter
CMV	conjugated meningococcal vaccines
CPCSEA	Committee for the Purpose of Control and Supervision of Experiments on Animals
CPPT	1-cyano-4 pyrrolidinopyridinium tetrafluoroborate
CRF	Case report form
CRM	cross reactive material
CRO	Contract research organization
CVD	Centre for Vaccine Development
DAIDS	Division of AIDS
DSMB	Data Safety Monitoring Board
ELISA	Enzyme linked immunosorbent assay
FDA	Food and Drug Administration (US)
FIH	first in human
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
GMTs	geometric mean titers
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICD	Informed consent document
ICF	Informed consent form
Ig	Immunoglobulin
IM	Intramuscular
IMD	invasive meningococcal disease
INDA	Investigational New Drug Application
IRB	Institutional review board
kg	Kilogram
mL	Milliliter
MedDRA	Medical Dictionary for Regulatory Activities
NIBSC	National Institute for Biological Standards and Control
NMT	Not more than

ABBREVIATION / ACRONYM	DEFINITION
PCR	Polymerase chain reaction
PHE	Public Health England
PI	Principal Investigator
PS	Polysaccharide
PT	Preferred term
q.s.	Quantum satis
rSBA	rabbit complement serum bactericidal activity
SAE	serious adverse event
SBA	serum bactericidal activity
SIIPL	Serum Institute of India Private Limited.
SOC	System organ class
SOP	Standard Operating Procedure
SRC	Safety Review Committee
TCMV	Tetravalent conjugate meningococcal vaccines
TT	tetanus toxoid
UK	United Kingdom
UMB	University of Maryland, Baltimore
USA	United States of America
w/v	Weight by volume
WHO	World Health Organization

PROTOCOL SIGNATURE PAGE

PATH, the study Sponsor, will keep a list of Investigator(s), who must provide a *Curriculum Vita* (CV) and a copy of their medical licenses to the Sponsor or Sponsor representatives. The Sponsor will keep a list and qualification records of all relevant Sponsor study personnel.

The Emmes Corporation will conduct site monitoring and provide medical monitoring, data management, statistical analysis, quality assurance, safety and pharmacovigilance services.

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"I have read the foregoing protocol and agree to conduct the study as outlined herein."

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STUDY SYNOPSIS

TITLE A Phase 1, double blind, randomized, controlled study to evaluate the safety and immunogenicity of a new Meningococcal Conjugate Vaccine containing serogroups A,C,Y,W and X in healthy adults
NAME OF THE STUDY VACCINE Meningococcal (A, C, Y, W, X) Polysaccharide Conjugated Vaccine (freeze-dried), also referred to as MCV-5
STUDY NUMBER ACYWX-001/ VAC-046
PROJECT PHASE Phase 1
SPONSOR PATH
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STUDY OBJECTIVES

Primary Objective:

To evaluate the safety of adjuvanted and non-adjuvanted formulations of MCV-5 vaccine.

Secondary Objectives:

To assess the immune response of adjuvanted and non-adjuvanted formulations of MCV-5 vaccine.

STUDY ENDPOINTS

Primary Endpoints

1. The occurrence and severity of solicited local and systemic post immunization reactions within seven days following vaccination.
2. The occurrence, severity, and relatedness to vaccination of unsolicited adverse events (AE) for 28 days following vaccination, and serious adverse events (SAE) for 6 months following vaccination.

Secondary Endpoints

1. The percentage of participants who show a seroconversion for Meningococcal Polysaccharide A, C, Y, W, and X specific antibodies, i.e. a ≥4-fold increase in post-immunization rabbit complement serum bactericidal activity (rSBA) titer with respect to pre-immunization rSBA titer, at 28 days after a single vaccine dose.
2. The percentage of participants who show a post-immunization seroprotection titer for Meningococcal Polysaccharide A, C, Y, W and X specific antibodies defined as rSBA titer of 1:8 and 1:128 at 28 days after a single vaccine dose.
3. Geometric mean titers (GMTs) of Meningococcal Polysaccharide A, C, Y, W, and X specific antibodies at 28 days after a single vaccine dose, as measured by rSBA assay.

STUDY HYPOTHESES

Primary hypothesis: Two formulations (adjuvanted and non-adjuvanted) of MCV-5 vaccine when given to healthy adults will be safe and well tolerated.

Secondary hypothesis: Two formulations (adjuvanted and non-adjuvanted) of MCV-5 vaccine when given to healthy adults will induce immune response to all the five serogroups of the vaccines.

STUDY DESIGN

This is a Phase 1, single center, double-blind, randomized, controlled clinical trial to be performed in 18 to 45 year old healthy volunteers.

The study will have three arms with three vaccines given in a 1:1:1 ratio: adjuvanted MCV-5, non-adjuvanted MCV-5 and Menactra®.

Each participant will receive a single intramuscular (IM) injection of one of the three vaccines and will be followed up for six months after the vaccination.

Safety evaluation will include safety laboratory parameters at baseline and seven days after vaccination, local and systemic post-immunization reactions for seven days after vaccination. Adverse events for one month after vaccination and serious adverse events for the entire study period (six months) will be collected.

The vaccinator will be aware of treatment allocation, although he/she will neither be able to influence or decide this allocation nor be part of the safety assessment. The study team involved in assessment of safety outcome as well as participants will be unaware of the group allocation.

STUDY RATIONALE

Currently, three polyvalent conjugate vaccines are available to protect against meningococcal disease. All three are tetravalent (serogroups A, C, W, and Y) vaccines; Menactra® (Sanofi Pasteur Inc.), Menveo® (Novartis) and Nimenrix® (GlaxoSmithKline Biologicals). There is vast experience with the use of these vaccines, which are generally well tolerated in all age groups. At this time,there is no licenced vaccine giving protection against meningococcal serogroup X which has caused many outbreaks in Africa and Europe in the recent past.

Following the MenAfriVac® MenA monovalent conjugate vaccine development experience, SIIPL has developed a candidate polyvalent conjugate vaccine composed of serogroups A, C, Y, W, and X *Neisseria meningitidis* capsular polysaccharides. The individual polysaccharides are conjugated to protein carriers, cross reactive material (CRM) or tetanus toxoid (TT), and formulated with or without aluminum phosphate (alum) as an adjuvant. The vaccine is intended for the prevention of meningitis and/or septicemia caused by serogroups A, C, Y, W, and X *N. meningitidis* in countries where the disease is endemic and causes large epidemics such as the countries in the African meningitis belt. The target population consists of infants, children and adults covering an age group of 9 months to 55 years.

This first-in-human (FIH) Phase 1 clinical study is designed to evaluate primarily the safety of the study vaccine. The three-group design will allow safety evaluation of the adjuvanted and non-adjuvanted MCV-5 formulations. The quadrivalent (ACYW) Menactra® vaccine has been chosen as a control vaccine comparator given the large safety database accumulated since the vaccine was introduced in the US in 2005, prequalified by World Health Organization (WHO) and progressively introduced in other countries.

The secondary objective of the study is immunologic evaluations of both adjuvanted and non-adjuvanted vaccine formulations.

STUDY VACCINES

MCV-5:

Two formulations (adjuvanted and non-adjuvanted) of the MCV-5 meningococcal conjugate vaccine will be used in the study. MCV-5 will be available as lyophilized product in a five dose vial containing meningococcal A and X polysaccharides conjugated to tetanus toxoid and meningococcal C, Y, and W polysaccharides conjugated to CRM.

The vaccine will be reconstituted with either normal saline (non-adjuvanted) or saline containing aluminum phosphate at 125 µg Al^{3+} /dose (adjuvanted) just prior to administration.

Composition of reconstituted final solution of one single 0.5 mL dose of adjuvanted MCV-5 vaccine

Vaccine component	Per 0.5 mL dose
Meningococcal A polysaccharide*	5 µg
Meningococcal C polysaccharide#	5 µg
Meningococcal Y polysaccharide#	5 µg
Meningococcal W polysaccharide#	5 µg
Meningococcal X polysaccharide*	5 µg
Sucrose	2.42 mg
Sodium Citrate	0.40 mg
Tris (Trometomol)	0.098 mg
Al^{3+}adjuvant	125 µg /dose
0.9% Sodium Chloride	q. s.
Tetanus Toxoid	7.8 to 33.4 µg.
CRM	11.7 to 50.1 µg

* - Each conjugated to Tetanus Toxoid (TT);
# - Each conjugated to CRM,
q.s. - Quantum satis

Composition of reconstituted final solution of one single 0.5 mL dose of non-adjuvanted MCV-5 vaccine

Vaccine component	Per 0.5 mL dose
Meningococcal A polysaccharide*	5 µg
Meningococcal C polysaccharide#	5 µg
Meningococcal Y polysaccharide#	5 µg
Meningococcal W polysaccharide#	5 µg
Meningococcal X polysaccharide*	5 µg
Sucrose	2.42 mg
Sodium Citrate	0.40 mg
Tris (Trometomol)	0.098 mg
0.9% Sodium Chloride	q. s.
Tetanus Toxoid	7.8 to 33.4 µg
CRM	11.7 to 50.1 µg

* - Each conjugated to Tetanus Toxoid (TT);
#- Each conjugated to CRM,
q.s. - Quantum satis

Menactra®:

Menactra® is a sterile, clear to slightly turbid liquid and each 0.5 mL dose is formulated in sodium phosphate buffered isotonic sodium chloride solution to contain four mcg each of meningococcal A, C, Y, and W polysaccharides conjugated to approximately 48 mcg of diphtheria toxoid protein carrier and residual amounts of formaldehyde of less than 2.66 mcg (0.000532%), by calculation.

STUDY PROCEDURES & VISIT SCHEDULE

After volunteers have signed the written informed consent, they will be screened for eligibility into the study. Screening will take place within 28 days prior to vaccination (Visit 1; Screening). A blood sample (up to 18 mL) will be taken at the screening visit for laboratory testing.

The following assessments will be conducted during the screening visit: medical history, physical examination, vital signs measurement and laboratory evaluation including hematology, serum chemistry and viral serology for Human immunodeficiency virus (HIV), Hepatitis B virus (HBV), and Hepatitis C virus (HCV). A test for pregnancy will be performed among females of child bearing potential. Inclusion/exclusion criteria will be assessed for eligibility.

At Visit 2 (Vaccination), eligible volunteers will be randomized in a 1:1:1 ratio to either one of the following groups:

Group	Vaccine
1 (n=20)	Adjuvanted Study vaccine (MCV-5)
2 (n=20)	Non-adjuvanted Study vaccine (MCV-5)
3 (n=20)	Reference vaccine (Menactra®, ACYW)

Baseline blood sample (20 mL) for immunogenicity testing will be collected before randomization on the day of vaccination and thereafter vaccine will be given as a single intramuscular injection of 0.5 mL in the deltoid. The day of vaccination will be considered as Day 1. After vaccination, participants will be observed for 60 minutes at the clinic to detect any immediate reactions or any other AE. All relevant information will be reported in the Case Report Form (CRF). A Memory Aid will be distributed and participants will be instructed to record post-immunization reactions, adverse events and concomitant medications. Participants will be informed to return to study centre for Visit 3 (Day 8).

At Visit 3 (Day 8), participants will undergo a targeted physical examination, vital sign measurement and a blood sample will be collected (up to 8 mL) to repeat the safety laboratory evaluations. Memory Aid records will be discussed with the participants, if needed, reconciled by the investigator/designee before recording in source document and transcribed into the CRF.

At Visit 4 (Day 29), the participants will undergo a targeted physical examination, vital sign measurement and review of interim health history, medication use and any report of adverse event through personal interview. A blood sample (30 mL) will be collected for immunogenicity evaluations. All the relevant information will be recorded into the CRF. The participant will be informed of the Visit 5 schedule.

At Visit 5 (85 days after vaccination), the participants will undergo targeted physical examination and review of interim medical history including medication use. All serious adverse events will be recorded into the CRF by the investigator/designee.

At Final study contact (180 ± 21 days after vaccination), the participant will be contacted by telephone to assess any serious adverse events that may have occurred.

STUDY DURATION

Participants will be followed for approximately six months after vaccination.

STUDY POPULATION

60 healthy male and female adult participants aged 18 to 45 years of age.

SAFETY ASSESSMENTS

Safety will be assessed during the study via the following parameters:

- Solicited local and systemic reactions for 7 days post-vaccination.
- Adverse events will be recorded for 28 days post vaccination.
- SAEs will be recorded for the study period of 180 days.

SAFETY MONITORING:

A Safety Review Committee (SRC) comprised of the Principal Investigator (PI), a medical expert with experience in vaccine pharmacovigilance not involved with the study, the Emmes medical monitor, Sponsor medical officer and SIIPL medical expert will be established to monitor participant safety throughout the duration of the study. The Emmes study statistician, with assistance of the data management staff, will prepare safety reports as needed for SRC discussions.

During the vaccination period, the SRC will review weekly the safety data. At any time during the study, the Emmes Coordinating Center will notify the SRC of ad hoc review if pause criteria may have been met.

The SRC reviews will be summarized with consensus recommendations to the study Sponsor as to whether there are safety concerns and whether the study should continue without change, be modified, paused or stopped. The SRC may request review of unblinded safety data by the vaccine pharmacovigilance expert in its deliberation. SRC consensus recommendations regarding modifying or stopping further enrolment may involve Sponsor consultation with the local regulatory authorities.

If at any time, a decision is made to discontinue administration of study product to all volunteers, expeditious notification will be provided by the sponsor to the US Food and Drug Administration (FDA), and by the PI to the University of Maryland, Baltimore (UMB) Institutional Review Board (IRB).

The following study pause rules will automatically pause or halt further vaccinations. However, volunteers already enrolled will continued to be followed for safety during the pause. These pause rules refer to suspected adverse reactions and will be triggered automatically if any of the event described below are met during the conduct of the study:

- One or more participants experience a serious adverse reaction.
- One or more participants experience a grade four injection site reaction.
- Two or more participants experience the same grade three injection site reaction.
- Two or more participants with the same severe (grade three) systemic reactogenicity signs or symptoms, within seven days following injection.
- Two or more participants experience the same vaccine-related grade three or higher clinical (including fever) or laboratory abnormality.

STATISTICAL CONSIDERATION:

Since this study is a Phase 1 trial, the sample size is designed to provide preliminary safety and immunogenicity data that may support testing the study product in larger adult cohorts or in age-descending studies.

With 20 vaccine recipients per group, this study's design allows a greater than 90% chance of observing an AE that has an 11% chance of occurrence. Conversely, if no AEs are observed in 20 vaccine recipients, the study will be able to rule out AEs occurring at a rate of approximately 14% based on the upper bounds of the one-sided 95% Confidence Interval (CI).

1. BACKGROUND AND INTRODUCTION

1.1. Pathogen

Among several different bacteria that can cause meningitis, *Neisseria meningitidis* (a gram-negative aerobic capsular bacterium, also referred as meningococcus), is known to cause large epidemics. *Neisseria meningitidis* otherwise a harmless commensal of human nasopharynx, under appropriate conditions is responsible for invasive meningococcal disease (IMD)–a spectrum of diseases that includes most commonly meningitis and fulminant septicaemia. Pneumonia, myocarditis, or pericarditis may also occur in IMD, albeit less commonly.[1, 2]

Once acquired, meningoccocci colonize the nasopharynx and patient may develop between the spectrum of an asymptomatic carrier state to a full blown IMD.[1]

Meningocci are classified into serogroups based on their capsular polysaccharides. Six of these serougroups viz. A, B, C, W, X, and Y are known to cause majority of IMD cases.[2]

These serogroups have the potential to cause large epidemics but this potential varies in each serogroup with respect to time and geographic location.[3] Serogroup A for example has been the most important cause of meningitis in sub-Saharan Africa and its outbreaks are commonest during December to June. On the other hand majority of IMD cases in Europe and USA are caused most commonly by serogroup B, followed by C and Y (Figure 1). Most recently cases of serogroup X are on the rise especially in Africa.[2, 4]

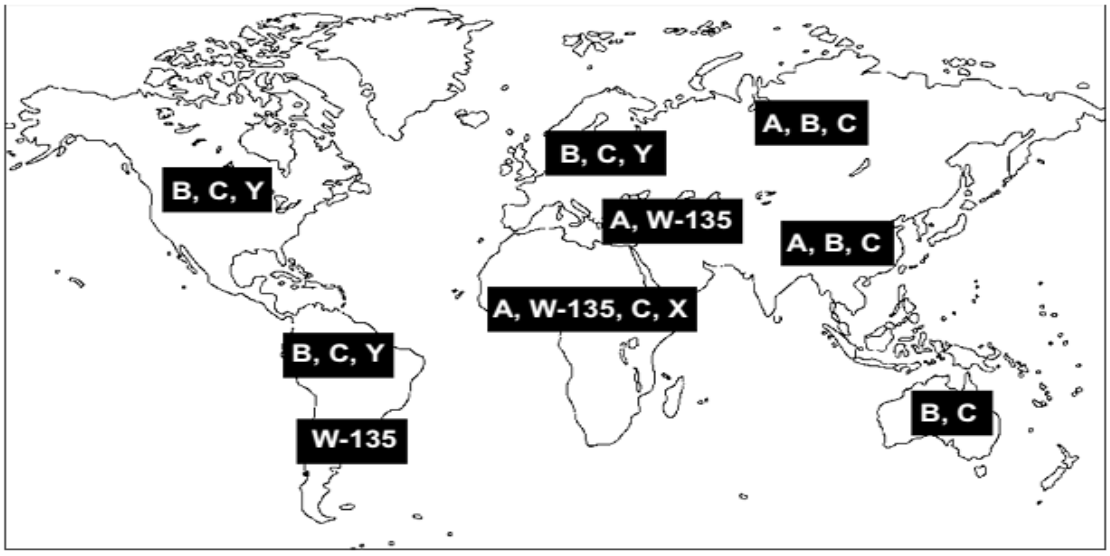


Figure 1: Global serogroup distribution of invasive meningococcal disease.[2]

1.2. Burden of Disease

Apart from serogroup variability, IMD also shows variation with respect to age groups with peak incidence occuring among children less than 2 years of age and adolescents between 16 and 21 years. During epidemics, disease rates show a shift towards older age groups.[2]

Meningococcal disease commonly alternates between an endemic situation of few isolated cases and fatal unpredictable epidemics in the African meningitis belt (a large area that spans sub-Saharan Africa from Senegal in the west to Ethiopia in the east).[5] This region has the highest annual incidence of IMD and is plagued with problem of recuring epidemics of large proportions. The incidence has been known to reach rates of up to 1000 cases per 100,000 people or 1% of the entire population.[3] This was seen during the large epidemics of 1996 and 2000 through 2001. In 1996 and 1997 there were > 250,000 cases, an estimated 25,000 deaths, and disability in 50,000 people. It is believed to be the largest epidemic in history. Similarly in the 2006 to 2007 epidemic season, there were 53,438 suspected cases and 3,816 deaths were reported to WHO from 15 African countries.[4]

Outside of the African meningitis belt, the incidence of IMD is significantly low, although there have been reports of outbreaks. In such areas any substantial increase in IMD cases above that which is expected at that place and time is considered as outbreak.[3, 4]

Respiratory droplets are the main source of meningococcal transmission and occurs most commonly due to close contacts with asymptomatic carrier.[6] Symptoms of IMD mainly include fever, loss of appetite, lethargy, vomiting, diarrhoea, photophobia and convulsions, and usually manifest 1 to 14 days after acquiring the pathogen.[1]

Meningococcal meningitis and fulminant septicemia—the two most serious presentations of IMD—may prove fatal in 50% of cases if untreated within 24 to 48 hours. Even when adequately treated, the mortality is close to 10%. Among the survivors of meningitis, it may cause in 10 to 20% of cases, severe permanent brain damage and sequelae such as mental retardation, deafness, epilepsy, or other neurological disorders.[2, 4]

1.3. Meningococcal Vaccines

The increasing resitance to antibiotics and associated escalation in healthcares costs makes vaccination as the best strategy to tackle invasive meningococcal disease.[2, 7]

1.3.1. Polysaccharide Vaccines

As depicted in Figure 2, the earliest vaccines against meningococci were discovered in the 1970s. The first ever meningococcal vaccine was developed against serogroup C as a response to recurring epidemics among military recruits in the USA. Eventually, further research led to availibility of vaccines against serogroups A, W, and Y. These were purified bacterial polysaccharide vaccines or “plain” polysaccharide vaccines that lacked conjugation.[8, 9]

Polysaccharide vaccines have an excellent safety profile and they have more than served their purpose of controlling outbreaks in military and other similar confined set ups. Later these vaccines were also used in endemic regions for prophylaxis.[2] Subsequently it was noted that the polysaccharide vaccines also showed good efficacy (> 85%) in older children and adults, however, they produced variable response among younger children (below 24 months of age) and often failed to provide protection in this population.[2, 8]

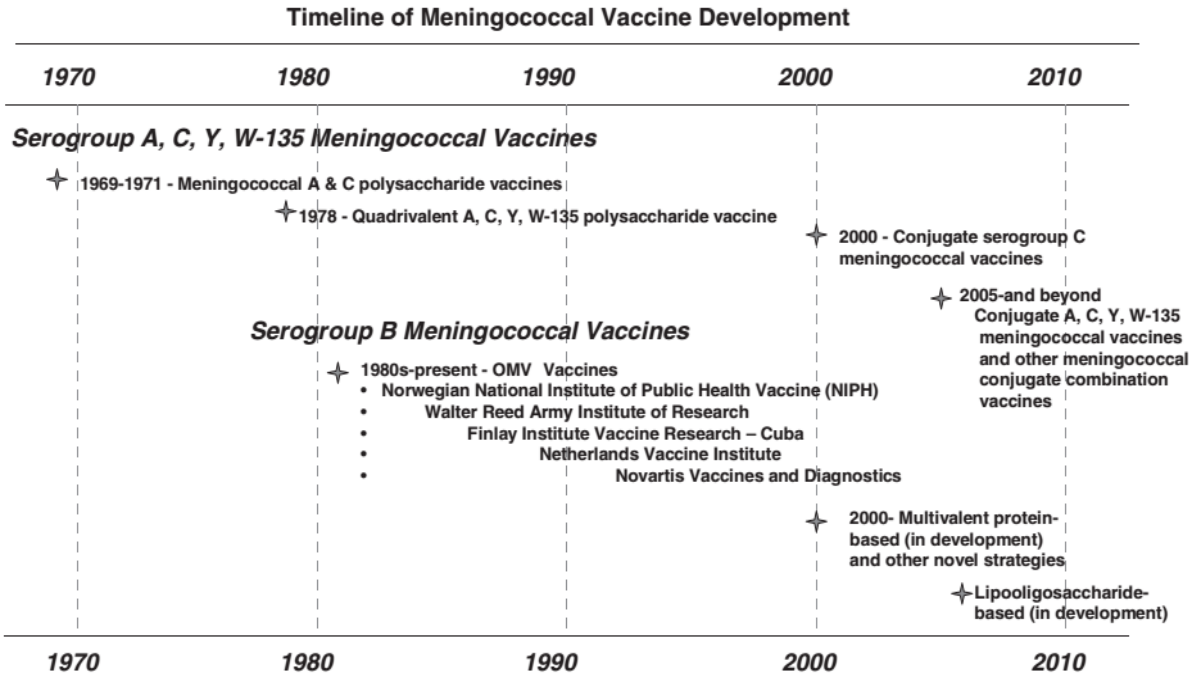


Figure 2: Timeline of meningococcal vaccine development.[8] OMV, outer membrane vesicle.
* Two serogroup B vaccines were approved in USA in late 2014 and early 2015.

Further, polysaccharide vaccines do not provide long term protection or immune memory. Instead they may induce immune hyporesponsiveness, particularly for serogroup C, on repeated administration. This is because of lack of T-cell induction by these vaccines, as a result of which the protection lasts for no more than three to five years post-vaccination.[7, 8] These vaccines also lack the ability to prevent organism transmission as they have no effect on pharyngeal carriage and do not confer herd immunity.[10-12]

Today, polysaccharide vaccines are licensed as bivalent (serogroups A and C), trivalent (serogroups A, C, and W-135), or quadravalent (serogroups A, C, Y, and W-135), although their availibility is very limited in most countries.[2] The drawbacks listed above made polysaccharide meningococcal vaccines unsuitable for use in population-scale interventions outside of epidemics and for infant immunization.[9] They are recommended in developed world for use in outbreaks related to specific strains, and as prophylaxis in susceptible travellers above 55 years of age as well as for military recruits.[13]

1.3.2. Conjugate Vaccines

The problems associated with the use of polysaccharide vaccines were overcome by the process of conjugation, wherein the capsular polysaccharide is conjugated to a highly immunogenic T-cell stimulating antigens such as CRM, diphtheria or tetanus toxoids. Vaccine against serogroup C was the first conjugated vaccine against meningococcal disease, that was developed in the 1990s in the United Kingdom.[9]

With their widespread use thereafter, conjugated meningococcal vaccines (CMV) proved superior to polysaccharide vaccines in eliciting T-cell responses and, thus, protected children less than

two years of age and induced immunologic memory. The advantage of immunologic memory is a booster response to subsequent doses of conjugate vaccines, a phenomena seen in all age groups. These vaccines also induce higher levels of protective titers and confer long-lasting protection. CMVs were also shown to overcome the problem of nasopharyngeal colonization and provide herd immunity. Furthermore, CMVs have not shown any hyporesponsiveness after repeated doses.[10, 11]

Currently, monovalent (A or C), and tetravalent (A, C, W-135 and Y) conjugate meningococcal vaccines are available to protect against IMD.

1.3.3. Monovalent Conjugated Vaccine against Meningococcal Serogroup C (MenCCV)

The monovalent vaccine against C serogrouop contains polysaccharide conjugated to the carrier diphtheria toxoid, CRM, or tetanus toxoid without preservatives. It is licensed for children aged > two months, adolescents and adults. Infants aged two to eleven months are given two doses (0.5 mL per dose) with at least two months between the doses, followed by a booster dose about one year later.[4]

The introduction of MenCCV in the routine infant immunization and a school-based “catch-up” in individuals up to 18 years of age in the United Kingdom (UK) resulted in reduction of 86.7% in the incidence of serogroup C within two years from 1999 to 2001. Number of associated deaths also fell from 67 in 1999 to 5 in 2001, thanks to MenCCV.[14] This prompted many other countries to introduce MenCCV in their immunization schedule with similar succes in controlling the sergroup C disease incidence.[9]

1.3.4. Monovalent Conjugated Vaccine against Meningococcal Serogroup A (MenAfriVac®)

The majority of the meningococcal epidemics in the African meningitis belt over the years have been caused by serogroup A with incidence rates as high as 500 cases per 100,000 population. In an effort to overcome this problem in a cost-effective way, the Meningitis Vaccine Project (MVP), a partnership between the WHO and PATH, was established with funding from the Bill and Melinda Gates Foundation.[15] The resultant product was a monovalent vaccine against A serotype called MenAfriVac® manufactured by Serum Institute of India Private Limited, and developed specifically to tackle the MenA epidemics in African Meningtis belt.[10]

MenAfriVac® is a lyophilized vaccine containing purified meningococcal A polysaccharide conjugated to tetanus toxoid.[2] The vaccine underwent an elaborate clinical development process that included a Phase 1 study in India, followed by seven Phase 2 and 3 studies conducted in India and the African meningitis belt.[16, 17]

The Phase 1 clinical study was conducted among 74 Indian adults (24 received MenAfriVac®, 25 a meningecoccal polysaccharide A and C vaccine, and 25 a tetanus toxoid vaccine) which involved a total of 48 weeks follow up for safety evaluation and four blood draws for testing immunogenicity (pre-immunization, and at 4 weeks, 24 weeks and 48 weeks post immunization). In the three vaccine groups, solicited reactions were mild and transient and resolved without sequelae with commonest being pain, redness, and swelling. All other adverse events resolved

without sequelae and were unrelated to the vaccines. Four weeks after vaccination 83% of subjects in MenAfriVac® group had a ≥ 4-fold increase in rSBA titers, 72% in the A/C group, and 12% in the tetanus toxoid only vaccine group. rSBA GMTs and group A specific IgG Enzyme linked immunosorbent assay (ELISA) geometric mean concentrations (GMCs) were also higher in MenAfriVac® groups as compared to A/C vaccine group (8,192 vs. 5,257 & 110 vs. 44 respectivley). Furthermore all subjects in the MenAfriVac® group who had initial four-fold increase in rSBA titers four weeks after vaccination remained four-fold responders one year later thus showing persistence in antibody response. In summary the vaccine was found to be safe and immunogenic.[18]

One of the Phase 2 clinical trials conducted among 12 to 23 month olds in Africa enrolled 601 subjects to receive either MenAfriVac® (n = 201), polysaccharide ACWY (Mencevax®) vaccine (n = 200) or *Haemophilus inlluenza* type b tetanus toxoid conjugated (Hib-TT) control vaccine (n = 200). There was no immediate safety issue at week four post-primary immunization, with all the local reactions reported being transient and resolved without sequelae. More indurations were reported in the MenAfriVac® group vs. the Mencevax® group (p = 0.01). Rates of other adverse events were similar between vaccine groups and they were unrelated to the study vaccines. Four weeks after vaccination 96% of subjects in the MenAfriVac® group had a ≥ 4-fold increase in Men A rSBA titer, 64% in the Mencevax® group and 36% in the Hib-TT vaccine group, whereas GMTs (rSBA) were 16 times greater after MenAfriVac® when compared with Mencevax® vaccine recipients. All but one subject in the MenAfriVac® group had a ≥ 4-fold increase in ELISA IgG concentrations, as compared to 78% in the Mencevax® group, and 4% in the Hib-TT group. Overall, the study MenAfriVac® showed antibody responses that are not inferior to those achieved by the Mencevax® vaccine.

Some of the subjects in this Phase 2 study were further followed up for 40 weeks, and 82% subjects in the MenAfriVac group still showed a ≥ 4-fold increase in rSBA titer vs. 38% in each of the other two groups. rSBA GMTs and ELISA GMCs were also higher in the MenAfriVac® group than the other two groups. MenAfriVac® group also had higher number of subjects with Men A rSBA titers ≥ 1:128 and 4-fold increase in ELISA specific IgG concentrations at 40 weeks. It was also found that the MenAfriVac® induced immunological memory since the subjects receiving booster at 40 weeks with either MenAfriVac® or polysaccharide vaccine showed highr GMTs (rSBA) if they were previously immunized with MenAfriVac®.

MenAfriVac® vaccine was thus found to be safe and it showed the characteristics of a conjugate vaccine with superior immunogenicity, effective inducement of immunological memory and inducement of bactericidal antibodies persisting at sustained levels after a single vaccine dose.[15]

Another Phase 2/3, among 900 healthy children and adults was conducted in Mali, The Gambia and Senegal to compare safety and immunogenicity of MenAfriVac® (n = 604) with that of Mencevax® vaccine (n = 296). Age of subjects at mmunization was 2 to 10 years (n = 302), 11 to 17 years (n = 301) and 18 to 29 years (n = 297). Safety evaluation at four weeks did not show any SAEs or deaths. Local and systemic reactions, AEs and SAEs were similar between vaccine groups overall as well as within each age group. Majority of the reactions were of mild or moderate intensity, transient and resolved without sequelae. During an additional one-year follow up, a total of five SAEs were reported and they were unrelated to study vaccines. A ≥ 4-fold increase in rSBA titer at four weeks post-immunization was seen in 78% in MenAfriVac® group vs. 46% in the

Mencevax® group. This remained consistent within each of the three age sub-groups. Even over a one year follow up MenAfriVac® group had a significantly higher sustained MenA antibody persistence. [15]

Another trial comparing the immunogenicity and safety of a single dose MenAfriVac® against the meningococcal group A component of polysaccharide vaccine (Mencevax®) at 28 days was conducted among 340 Indian children (169 in MenAfriVac® group) aged 2 to 10 years. Results showed 95.2% of children in MenAfriVac® group had a ≥4-fold response in rSBA as compared to 78.2% in the Mencevax® group. Almost all children in both vaccine groups had a ≥4-fold response in group A-specific IgG concentration but the IgG GMC was significantly greater in the MenAfriVac® group. Local and systemic reactions during the four days after immunization were similar for both vaccine groups except for tenderness (30.2% in MenAfriVac® group vs. 12.3% in Mencevax® group). None of the adverse events or serious adverse events were related to the study vaccines.[19]

The vaccine was subsequently licensed in 2009 and was prequlaified by WHO in 2010. Since then it has been widely used in over 217 million individuals of 1 to 29 years of age and has been found to be highly effective and safe.[3, 20-23]

Use of MenAfriVac® has been highly effective at preventing IMD of serogroup A, reducing it by nearly 100%, eliminating outbreaks as well as decreasing carrier states.[20, 24] It also reduced the incidence in those too young or too old to have been vaccinated, demonstrating an additional indirect herd effect. In the data generated for two years since its use started in three African countries viz. Burkina Faso, Mali and Niger, there have been no cases of MenA disease reported in vaccinated population.[10]

1.3.5. Tetravalent Conjugate Meningococcal Vaccines (TCMV)

Today, three different brands of TCMV are available viz. Menactra® (Sanofi), Menveo® (Novartis) and Nimenrix® (Glaxo SmithKline Beecham) with each brand having serogroups A, C, W, an Y but conjugated to different proteins.[2, 25-27]

Menactra®, first ever TCMV uses diphtheria toxoid as conjugate, whereas Menveo® and Nimnerix® use CRM and Tetanus Toxoid respectively for conjugation of polysaccharides. Menactra®, Menveo® and Nimenrix® are licensed for use in individuals upto 55 years of age. The lower limit of age for Menactra® is 9 months, Menveo® is 2 months and Nimenrix® is 12 months.[25-27]

For individuals aged 11 years and above, a single dose of either Menactra® or Menveo® should be administered at age 11 or 12 years, with a booster dose at age 16 years of age. Booster dose of Nimenrix® is not recommended. Those aged 2 to 23 months are given Menveo® as four-dose series till six months of age or a two-dose series if above that age. Whereas Menactra® should be used as a two dose series starting at nine months with a minimun three months before the second dose.[25-27]

Use of TCMV has been associated with excellent safety and immunogenicity profile, with reduction in incidence of meningococcal diseases in regions where they have been introduced for routine immunization.[4]

1.3.6. Overall Impact of Meningococcal Vaccines

The widespread use of conjugate meningococcal vaccines especially in higly endemic settings and at population level has reduced the burden of IMD drastically since pre-vaccination era. Inspite of this, the use of conjugate vaccine is still a big hurdle in developing world due to its high cost. Unlike Men A vaccine which was specifically developed for the Meningitis belt in Sub-Saharan Africa and hence was very cost effective, the tetravalent vaccine still remains elusive for that kind of application in this region.[9, 28]

1.3.7. Vaccine against B Serogroup

Serogroup B meningococcus has a poorly immunogenic capsule and contains epitopes that potentially cross-react with human antigen, which has hindered progress on developing a polysaccharide vaccine effective against it.[4, 29]

Recently, though, the FDA of USA has licensed two serogroup B meningococcal vaccine viz. Trumenba® and Bexsero® for use in people 10 to 25 years of age as a three-dose series and two-dose series respectively.[30-32]

1.3.8. Vaccine against X Serogroup

There is no vaccine available which gives protection against serogroup X which has caused many outbreaks in Africa and Europe in recent past.[33] The WHO has expressed concerns over the lack of such a vaccine and has encouraged more research into it.[4]

1.4. Study Vaccine

Currently, there is no vaccine available against serogroup X of *N. meningitidis*. This bacterium has caused many outbreaks in Africa and Europe in recent past. The serogroup X has been responsible for outbreaks between 2006 and 2010 in Kenya, Niger, Togo, Uganda, and Burkina Faso, the latter with at least 1,300 cases of serogroup X meningitis among the 6,732 reported annual cases.[33]

As a result, SIIPL has developed the candidate vaccine MCV-5, which is a polyvalent conjugate vaccine composed of serogroups A, C, Y, W, and X of *Neisseria meningitidis* capsular polysaccharides, conjugated to protein carriers, CRM and tetanus toxoid, with aluminum phosphate as an adjuvant. It is intended for the prevention of meningitis and/or septicemia caused by serogroups A, C, Y, W, and X *N. meningitidis* in countries where the disease is endemic and causes large epidemics such as the countries in the African meningitis belt. The target population consists of infants and children and adults aged 1 to 55 years.

1.5. Summary of Nonclinical Studies

Table 1: Preclinical Studies

Study Title	Study Site	Study Type & Compliance	Animal Model	Sections in the protocol
A 5-week subcutaneous dose-ranging immunogenicity study of monovalent meningococcal serotype X polysaccharide conjugate (MenX-TT) with and without aluminum phosphate adjuvant in mice	SIIPL	Immunogenicity Non-GLP	Swiss albino mice	1.5.3.1
A 7-week subcutaneous immunogenicity study of the MenX-TT component in the MCV-5 presentation with and without aluminum phosphate adjuvant in mice.	National Institute for Biological Standards and Control, London (NIBSC), United Kingdom	Immunogenicity Non-GLP	BALB/c mice	1.5.3.2
A 5-week intramuscular immunogenicity study of candidate SIIPL MCV-5 vaccine formulations in comparison to commercial vaccine in rabbits	SIIPL	Immunogenicity Non-GLP	New Zealand white rabbits	1.5.3.3
A 5-week intramuscular dose-ranging immunogenicity study of pentavalent SIIPL MCV-5 vaccine (tox formulation) with and without aluminum phosphate adjuvant in rabbits	SIIPL	Immunogenicity Non-GLP	New Zealand white rabbits	1.5.3.4
A 7-week intramuscular toxicity study of [pentavalent] meningococcal (A,C,Y,W,X) polysaccharide conjugate vaccine (freeze-dried) in New Zealand white rabbits with a 6-week recovery	MPI Research, Inc., 54943 North Main Street Mattawan, MI 49071-8353, U.S.A.	Toxicity & immunogenicity study. GLP	New Zealand white rabbits	1.5.2.1 & 1.5.3.5
Series of toxicology studies of 4-Pyrrolidinopyridine (4-PP, a byproduct of CPPT conjugation chemistry)	MPI Research, Inc., 54943 North Main Street Mattawan, MI 49071-8353, U.S.A. and BioReliance, Rockville, MD, U.S.A.	Byproduct toxicology. Mutagenicity GLP	Rats, guinea pigs, prokaryotic & eukaryotic cells	1.5.2.2

1.5.1. Non-Good Laboratory Practice (GLP) Nonclinical Pharmacology/Proof of Concept Studies

Not Applicable

1.5.2. Toxicology Studies

Pre-clinical GLP toxicology study

A repeated dose GLP toxicology study was conducted in 60 rabbits at a GLP certified testing facility, MPI Research, Inc, 54943 North Main Street, Mattawan, MI, 49071-8353, USA. The study comprised of three groups of animals receiving 4 doses of either MCV-5 vaccine (5 µg of each serogroup antigen) with aluminum phosphate adjuvant, MCV-5 vaccine without adjuvant, or saline control administered 2 weeks apart. All animals survived to the scheduled necropsy. There were no test article-related effects noted for clinical observations, ophthalmoscopic findings, body weights, body weight gains, food consumption, or body temperatures. No test article-related alterations were observed in hematology, coagulation, or urinalysis parameters. There were no clear and consistent organ weight changes seen in terminal or recovery animals. Mild injection site reactions included very slight edema and very slight erythema. These were consistent with injection of a vaccine and comparable to control animals injected with normal saline. Test article-related microscopic findings were seen at the injection sites for all terminal and recovery groups. The injection site findings were not considered to be adverse, given the low severity, lack of systemic findings, limited serum chemistry findings, and lack of associated clinical findings. At recovery, at all injection sites, there was a strong trend towards recovery in all groups, with generally reduced incidence and severity of most findings compared to terminal groups. At recovery, at all injection sites, there was a strong trend towards recovery in all groups, with generally reduced incidence and severity of most findings compared to terminal groups.

Toxicology study of 4-PP (a byproduct of CPPT conjugation chemistry [in progress])

A set of toxicology studies, of 4-PP, a residual in 1-cyano-4 pyrrolidinopyridinium tetrafluoroborate (CPPT) conjugation, was also conducted at MPI Research, Inc and BioReliance under subcontract to MPI. These included:

a) Oral single dose in rats
b) IM single dose in rats
c) In vitro mutagenicity, prokaryotic cells
d) In vitro mutagenicity, eukaryotic cells (mouse lymphoma)
e) Skin sensitization study in guinea pigs

The studies on 4-PP suggest that this by-product is not mutagenic or clastogenic in standard genotoxicity assays, is well tolerated after a single intramuscular injection in rats and does not cause dermal sensitization in guinea pigs.

Test article related clinical observations at oral doses of 10 and 50 mg/kg included piloerection, audible breathing, and vocalization whereas decreased activity, ataxia, tremors, and low carriage at dose of 50 mg/kg. Animals in 200 mg/kg oral dose were either euthanized in extremis or found dead on Day 1.

The No-Observed-Adverse-Effect-Level (NOAEL) of 4-PP is considered to be 10 mg/kg following oral administration and 0.2 mg/site following intramuscular administration. In comparison, the content of 4-PP in MCV-5 vaccine is estimated to be less than 500 nanogram per dose of vaccine. This value is considerably lower than the NOAEL.

Additional details of these toxicology studies are available in the investigator’s brochure (IB).

1.5.3. Immunogenicity Studies

Immunogenicity study of monovalent MenX tetanus toxoid conjugate vaccine (MenX-TT) in mice

This study was conducted in Swiss albino mice at SIIPL, India. The study results presented in Table 2 show that immunization with MenX-TT PS conjugate elicits antibody responses to MenX PS, as measured by both IgG immunoassay and rSBA. IgG responses were low and rSBA antibody responses were undetectable for the group of mice immunized with adjuvanted native MenX PS (Group 1, Table 2). Immunization with either 0.5 µg or 1.0 µg of MenX-TT conjugate was highly immunogenic and generated strong bactericidal activity after three doses (Days 0, 14, 28), suggestive of a T-cell dependent immune response. The addition of aluminum phosphate adjuvant further improved IgG and rSBA titers, particularly at the 0.5 dose level (Groups 3 and 4, Table 2). These data suggest that that the MenX-TT conjugate is immunogenic and could be included in a polyvalent meningococcal conjugate vaccine.

Table 2: Day 35 Serum IgG Titers to MenX after Three Immunizations with MenX-TT

Group	Treatment	Amount per dose (µg)	IgG titer (GMT)	rSBA titer (GMT)
1	Saline	-	50	<4
2	Native MenX PS + aluminum phosphate	0.5 + 125	1,600	4
3	MenX-TT conjugate	0.5	6,400	42
4	MenX-TT conjugate + aluminum phosphate	0.5 + 125	40,637	128
5	MenX-TT conjugate	1.0	51,200	341
6	MenX-TT conjugate + aluminum phosphate	1.0 + 125	51,200	512

Immunogenicity of the MenX-TT Component of MCV-5 Vaccine in BALB/c Mice

This study was conducted in BALB/c mice at National Institute for Biological Standards and Control (NIBSC), UK, to confirm and further evaluate the immunogenicity of the MenX-TT PS conjugate antigen, with and without aluminum phosphate adjuvant, when combined with the other four meningococcal PS conjugates (MenA-TT, MenC-CRM, MenY-CRM and MenW-CRM) intended to be included in the pentavalent SIIPL MCV-5. Groups of 20 young adult female BALB/c mice were immunized subcutaneously with either MCV-5 with aluminum phosphate or MCV-5 without adjuvant or licensed quadrivalent Menveo® PS conjugate vaccine as a control. Vaccination was on days 0, 14, 28 with each mouse receiving 1/10th of a human dose of the test vaccines at each time point

As expected, the antibody titers to MenX for the animals that were immunized with Menveo®, which does not contain a MenX PS conjugate component, were low at all bleed time points (Study Days 14, 28, and 42) and reached a maximum relative log GMT of 1.45 units/mL at study day 42 (2 weeks post-3rd dose) as presented in Table 3. An increase in MenX-specific antibody titers was observed in animals immunized with MCV-5 and without aluminum phosphate following the second dose, and additional increases were observed after the third dose. Additionally, the MenX-specific antibody responses to MCV-5 with aluminum phosphate adjuvant were higher than those to MCV-5 without adjuvant, and this difference was most pronounced at study day 42 (post

dose 3). Taken as a whole, these results clearly demonstrate that the MenX-TT antigen is robustly immunogenic when combined with the other four polysaccharide conjugate antigens (MenACYW) in MCV-5 and that addition of aluminum phosphate adjuvant improves its immunogenicity.

Table 3: Geometric Mean Serum IgG Titers to MenX

Group	Vaccine Treatment	Day 14	Day 28	Day 42
		GMT (95% CI)	GMT (95% CI)	GMT (95% CI)
1	MCV-5 (Adjuvanted)	0.29 (0.11 – 0.82)	43.89 (19.31-99.75)	140.23 (96.49-203.81)
2	MCV-5 (Unadjuvanted)	0.33 (0.17-0.65)	34.05 (17.19-67.45)	63.39 (47.60-84.42)
3	Menveo®	0.02 (0.02-0.04)	0.74 (0.29-1.89)	1.45 (1.11-1.89)

Immunogenicity of Candidate SIIPL MCV-5 Formulations in New Zealand White Rabbits

The immunogenicity of three different candidate formulations of adjuvanted SIIPL MCV-5 were evaluated in New Zealand white rabbits in a study conducted at SIIPL. The adjuvanted F3 formulation selected for clinical development had the best immunogenicity profile compared to the other two adjuvanted formulations (F2 and F4). Additionally, the adjuvanted F3 formulation elicited comparable or better immune responses to serotypes MenA, C, Y and W than did Menveo® (Tables 4 and 5). Additional details of this study are available in the IB.

Table 4: Geometric mean IgG titers to MenA,C,Y,W and X

Vaccine Treatment	Study Day	rSBA antibody responses (GMTs)				
		MenA	MenC	MenY	MenW	MenX
Menveo®	0	50	50	50	50	*n.d.* [a]
	35	44,572	25,600	38,802	29,047	*n.d.* [a]
SIIPL MCV-5 F2 with aluminum phosphate adjuvant	0	50	50	50	50	50
	35	72,408	51,200	72,408	60,887	60,887
SIIPL MCV-5 F3 with aluminum phosphate adjuvant	0	50	100	50	50	200
	35	58,813	58,813	117,627	89,144	51,200
SIIPL MCV-5 F4 with aluminum phosphate adjuvant	0	50	100	50	50	50
	35	33,779	9,701	29,407	25,600	51,200

[a] *No data (n.d.) because Menveo® does not contain a MenX component.*

Table 5: Geometric mean bactericidal antibody titers to MenA,C,Y,W and X

Vaccine Treatment	Study Day	rSBA antibody responses (GMTs)				
		MenA	MenC	MenY	MenW	MenX
Menveo®	0	2	2	4	2	*n.d.*[a]
	35	446	223	256	223	*n.d.*[a]
SIIPL MCV-5 F2 with aluminum phosphate adjuvant	0	2	2	2	2	16
	35	724	215	152	256	1,024
SIIPL MCV-5 F3 with aluminum phosphate adjuvant	0	2	2	2	2	8
	35	676	512	388	588	1,024
SIIPL MCV-5 F4 with aluminum phosphate adjuvant	0	2	2	2	2	2
	35	338	64	111	147	676

[a] *No data (n.d.) because Menveo® does not contain a MenX component.*

Immunogenicity of the SIIPL MCV-5 vaccine in New Zealand White Rabbits

The immunogenicity of the first cGMP lot of the pentavalent SIIPL MCV-5 vaccine was also evaluated in New Zealand white rabbits at SIIPL. Groups of adult New Zealand white rabbits were dosed with either MCV-5 reconstituted with diluent with and without 125 µg aluminum phosphate adjuvant, the licensed quadrivalent vaccine Menactra® or the licensed quadrivalent vaccine Menveo®. The dose of MCV-5 was 5 µg per PS conjugate component in the vaccine. The dose of Menactra® was 4 µg per PS conjugate component in the vaccine. The dose of Menveo® was 10 µg of MenA PS conjugate and 5 µg each for the MenC, Y and W PS conjugate components in the vaccine. Animals were immunized by intramuscular injection on Days 0, 14 and 28.

In summary, the IgG and bactericidal (rSBA) antibody response results from this study clearly demonstrate that MCV-5 was strongly immunogenic for all 5 meningococcal serotypes (A, C, Y, W and X) represented in the vaccine and that addition of aluminum phosphate adjuvant improved its immunogenicity. Additionally, adjuvanted MCV-5 had comparable or better immunogenicity for the meningococcal serotypes A, C, Y, and W than the licensed vaccines Menveo® and Menactra®. Additional details of this study are available in the IB.

MPI rabbit immunogenicity study of all five serogroups

This GLP study evaluated the immunogenicity of adjuvanted and non-adjuvanted MCV-5 vaccine in adult New Zealand White rabbits following four bi-weekly intramuscular doses given for seven weeks in rabbits and after a six-week recovery period. Immunogenicity was measured by rSBA with regards to titers of IgG antibodies against all five serogroups in serum samples collected on Days 1 and 43. A third group of rabbits received saline as control. The sample size in each of the groups was 20 (10 males and 10 females).

For all three groups, no IgG responses were seen from the Day 1 pre-immune sera against any of the meningococcal serogroups. The Day 43 saline control Group 1 had similar geometric mean IgG concentrations to those obtained in the Day 1 pre immune sera across all serogroups. The Day 43 group immunized with MCV-5 vaccine with or without adjuvant gave a response against all serogroups that was significantly greater than the saline control group.

Higher antibody concentrations were observed in sera when aluminum phosphate was used as an adjuvant, with increases ranging from 49% to 165%. Serogroups A, Y, and X all showed a statistically significant increase in antibody concentration compared to the group without adjuvant. However, for serogroups C and W, this observed difference between the two groups did not reach statistical significance. Additional details of this study are available in the IB.

In summary, this study showed that the MCV-5 pentavalent vaccine formulation produced a strong immune response against all five serogroups. The addition of adjuvant resulted in an increase in immune response for all five serogroups with a statistically significant increase for three serogroups.

1.6. Clinical Studies

No human data is available as of now and the present first-in-human study on MCV-5 vaccine is being conducted with primary objective of assessing the vaccine's safety in an adult population.

There is no clinical data available on potential safety risks, although it is anticipated that the vaccine will have a safety profile similar to that of currently licensed vaccines against meningococci including Menactra® (reference vaccine in present study) and MenAfriVac®.

Apart from local solicited reactions such as pain, erythema, induration and swelling, other common (≥10%) solicited systemic reactions in adults (18 to 55 years) who received Menactra® included headache, malaise, fatigue, arthralgia, diarrhea and anorexia.[26] Solicited reactions were considered those occurring within seven days of vaccination.

Clinical trial of MenAfriVac® conducted in 18 to 29 year olds showed post vaccination local and systemic reactions to be comparable to Menveo® with headache as the most commonly reported reactions (12%) followed by tenderness (6%). Other reactions such as fever, vomiting, fatigue, myalgia and arthralgia were infrequent (2.5% to less than 1%).[34]

2. HYPOTHESIS, SCIENTIFIC RATIONALE, OBJECTIVES AND STUDY DESIGN

2.1. Study Hypotheses

The proposed Phase 1 study will test the following hypotheses:

a. Primary hypothesis: Two formulations (adjuvanted and non-adjuvanted) of MCV-5 vaccine when given to healthy adults will be safe and well tolerated.

b. Secondary hypothesis: Two formulations (adjuvanted and non-adjuvanted) of MCV-5 vaccine when given to healthy adults will induce immune response to all the five serogroups of the vaccines.

2.2. Scientific Rationale

Currently, three conjugate polyvalent vaccines are available to protect against meningococcal disease. All three are tetravalent (serogroups A, C, W and Y) vaccines; Menactra® (Sanofi Pasteur Inc.), Menveo® (Novartis) and Nimenrix® (Glaxo SmithKline Beecham). There is large experience with the use of these vaccines, which are generally well tolerated in all age groups. At this time, there is no licenced vaccine giving protection against serogroup X which has caused many outbreaks in Africa and Europe in recent past.

Following the MenAfriVac® MenA monovalent conjugate vaccine development experience, SIIPL has developed a candidate polyvalent conjugate vaccine composed of serogroups A, C, Y, W and X *Neisseria meningitidis* capsular polysaccharides. This candidate MCV-5 is conjugated to protein carriers, CRM and tetanus toxoid, and formulated with or without aluminum phosphate as an adjuvant. It is intended for the prevention of meningitis and/or septicemia caused by serogroups A, C, Y, W, and X *N. meningitidis* in countries where the disease is endemic and causes large epidemics such as the countries in the African meningitis belt. The target population consists of infants, children and adults aged 1 to 55 years.

This first Phase 1 clinical study is designed to evaluate primarily the safety of the study vaccine. The three-group design of the study will allow safety evaluation of the adjuvanted and non-adjuvanted MCV-5 formulations. The Menactra® vaccine has been chosen as control vaccine for the large safety database accumulated since the vaccine has been introduced in the USA in 2005 and progressively in other countries.[9, 35]

In addition, secondary immunogenicty evaluation is planned on both adjuvanted and non-adjuvanted formulations.

This Phase 1 study will be performed in adult healthy volunteers aged 18 to 45 years of age.

2.3. Overall Clinical Development Strategy

SIIPL has developed MCV-5 with an aim to license and make it available particularly in developing markets including Africa. Once the results of current study are available, both the adjuvanted and non-adjuvanted formulations will further be compared for immune response in a Phase 2 clinical trial among toddlers. Results of this Phase 2 study will help decide which one of the formulations to be carried into the next phases of clinical development.

2.4. Study Design

This is a Phase 1, single center, double-blind, randomized, controlled clinical trial to be performed in 18 to 45 year old healthy volunteers.

The study will have three arms with three vaccines given in a 1:1:1 ratio: adjuvanted MCV-5, non-adjuvanted MCV-5 and Menactra® given as a single intramuscular injection. All participants will be followed up for six months after the vaccination.

2.4.1. Discussion of Study Design

The three-group design of the study will allow comparison of the adjuvanted and non-adjuvanted ACYWX safety profile with that of a licensed ACYW conjugate vaccine (reference vaccine group).

The vaccinator will be aware of group allocation, although he/she will not be able to influence or decide this allocation nor be part of the safety assessment. This will ensure that the study team, involved in assessment of safety outcome as well as participants, are unaware of the identity of study vaccine administered to them. This will help rule out the bias at the time of assessment.

As the reference product and study vaccines are different in appearance and composition, the vaccinator blind cannot be maintained in this study. However the vaccinator is not involved in safety assessment.

In addition, immunogenicity assessments are planned to evaluate any difference in the immune responses induced by the adjuvanted and non-adjuvanted study vaccines and to compare against the reference vaccine. The study, however, is not statistically powered to determine significance of any difference. There is neither any formal sample size calculation as this is a Phase 1 trial.

As this is the first clinical study with the study vaccine, the study will be initially performed in adult healthy volunteers.

2.4.2. Primary Objective

To evaluate the safety of adjuvanted and non-adjuvanted formulations of MCV-5 vaccine.

2.4.3. Secondary Objective

To assess the immune response of adjuvanted and non-adjuvanted formulations of MCV-5 vaccine.

2.4.4. Primary Endpoints

- The occurrence and severity of solicited local and systemic post immunization reactions within seven days following vaccination.
- The occurrence, severity, and relatedness of unsolicited adverse events for 28 days following vaccination, and serious adverse events for 6 months following vaccination.

2.4.5. Secondary Endpoints

- The percentage of participants who show a seroconversion for Meningococcal Polysaccharide A, C, Y, W and X specific antibodies, i.e. a ≥4-fold increase in post-immunization rSBA titer with respect to pre-immunization rSBA titer, at 28 days after a single vaccine dose.
- The percentage of participants who show a post-immunization seroprotection titer for Meningococcal Polysaccharide A, C, Y, W, and X specific antibodies defined as rSBA titer of 1:8 and 1:128 at 28 days after a single vaccine dose.
- GMTs of Meningococcal Polysaccharide A, C, Y, W and X specific antibodies at 28 days after a single vaccine dose, as measured by rSBA assay.

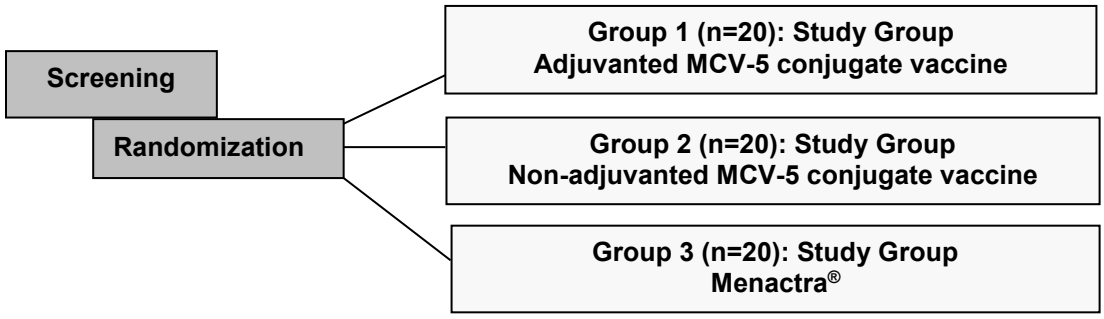
2.4.6. Exploratory Endpoints

Additional immune response of adjuvanted and non-adjuvanted formulations of MCV-5 may be assessed by other relevant assays if remaining specimen volume is adequate.

2.4.7. Randomization and Vaccination

This is a prospective, randomized, parallel group, double blind clinical study. For arm allocation, a randomization-blocking scheme (1:1:1) will be used. Each block will be of six participants. The vaccine will be supplied to the study site while respecting the randomization block size.

The vaccine will be administered sequentially depending upon the randomization number by unblinded clinical staff not involved with the clinical assessment of study participants. Other investigative site personnel will not be aware of which group the participant has been randomized. The identity of the same cannot be revealed except in an emergency. Study monitor will verify randomization by checking the treatment allocation against the vaccination records at each study visit.



3. STUDY PRODUCTS

3.1. Test Vaccine (MCV-5)

3.1.1. Product Description

Serum Institute of India Private Limited's candidated vaccine MCV-5 is a sterile pentavalent polysaccharide-conjugate vaccine composed of serogroups A, C, Y, W and X *Neisseria meningitidis* capsular polysaccharides, conjugated to two different protein carriers, with aluminum phosphate as an adjuvant. Serogroup A & X polysaccharide are separately conjugated to tetanus toxoid while C, Y & W are separately conjugated to recombinant CRM (CRM is genetic mutant of diphtheria toxin).

It is intended for intramuscular administration and protects against meningitis and/or septicemia caused by serogroups A, C, Y, W, and X *N meningitidis.*

N. meningitidis A, C, Y, W, and X polysaccharides are produced by cultivating cells in fed batch fermentation and purified after separation. Tetanus toxin is derived from *Clostridium tetani* grown in a modified medium and purified. CRM is expressed by *Pseudomonas fluorescens* strain and used after it is purified. Meningococcal polysaccharides are covalently conjugated to TT or CRM and purified to make the final formulated vaccine.

3.1.2. Manufacturer

Serum Institute of India Private Limited, Pune

3.1.3. Presentation and Formulation

The MCV-5 vaccine is provided as a freeze-dried powder in a five-dose vial containing meningococcal A, C, Y, W, and X polysaccharides conjugated to tetanus toxoid and CRM protein. The vaccine has to be reconstituted with either adjuvant containing diluents or 0.9% Sodium Chloride Injection, USP as per sections 3.2 and 3.4. (Further details regarding preparation of adjuvanted and non-adjuvanted MCV-5 are provided in the protocol specific Pharmacy Manual.) No preservative is added either in vaccine or diluents component during manufacture.

Vaccine Composition of 5 dose vial of MCV-5 vaccine (freeze dried)

Component	Quantity
Meningococcal A polysaccharide*	30 μg
Meningococcal C polysaccharide#	30 μg
Meningococcal Y polysaccharide#	30 μg
Meningococcal W polysaccharide#	30 μg
Meningococcal X polysaccharide*	30 μg
Sucrose	15 mg
Sodium Citrate	2.5 mg
Tris (Trometomol)	0.61 mg

* - Conjugated to Tetanus Toxoid (TT); # - Conjugated to CRM; q.s. - Quantum satis

3.1.4. Stability and Storage

MCV-5 vaccine must be stored between +2°C to +8°C.

3.2. Diluents

3.2.1. Adjuvanted Diluent

Product Description

The adjuvanted diluent containing aluminum phosphate used to prepare the adjuvanted MCV-5 is a sterile white homogeneous suspension presented in a glass ampoule.

Manufacturer

Serum Institute of India Private Limited, Pune

Presentation and Formulation

The adjuvant containing diluent is provided in a five-dose glass ampoule containing an actual fill volume of 3.1 mL ± 0.1 mL. Each 0.5 mL of adjuvanted diluent contains 125 µg Al3+ formulated in 0.9% Sodium Chloride.

Stability and Storage

The adjuvanted diluent must be stored between +2°C to +8°C and not to be frozen.

3.2.2. Non-Adjuvanted Diluent

0.9% Sodium Chloride Injection, USP, will be used to prepare the non-adjuvanted MenACYWX vaccine. The research pharmacy at the site will procure enough supply of the same lot of 0.9% Sodium Chloride Injection to complete the study. The 0.9% Sodium Chloride Injection will be stored at 20°C - 25°C.

3.3. Reference Vaccine (Menactra®)[26]

3.3.1. Product Description

Menactra® is a sterile, intramuscularly administered quadrivalent conjugate vaccine composed of serogroups A, C, Y, and W *Neisseria meningitidis* capsular polysaccharides, conjugated to a protein carrier, diphtheria toxoid protein, without any adjuvant. It is intended for the prevention of meningitis and/or septicemia caused by serogroups A, C, Y, and W *N. meningitidis*.

N. meningitidis A, C, Y, and W-135 strains are cultured on Mueller Hinton agar and grown in Watson Scherp media containing casamino acid.

3.3.2. Manufacturer

Sanofi Pasteur Inc.

3.3.3. Presentation and Formulation

Menactra® vaccine is a clear to slightly turbid solution supplied in 0.5 mL single dose vial. Each 0.5 mL dose of vaccine is formulated in sodium phosphate buffered isotonic sodium chloride solution to contain four mcg each of meningococcal A, C, Y, and W-135 polysaccharides conjugated to approximately 48 µg of diphtheria toxoid protein carrier and residual amounts of formaldehyde of less than 2.66 µg (0.000532%), by calculation.

3.3.4. Stability and Storage

Menactra® must be stored between +2°C to +8°C.

3.4. Preparation and Administration

Participants will be randomized 1:1:1 to receive either adjuvanted MCV-5 or non-adjuvanted MCV-5 or Menactra®. The vaccination will be administered by a staff not involved with the clinical assessment of study participants.

3.4.1. Adjuvanted MCV-5

The adjuvanted MCV-5 is prepared by reconstituting one vial of MCV-5 with a single ampoule of adjuvant containing diluent. For each participant, 0.5 mL dose will be withdrawn from the reconstituted five-dose adjuvanted MCV-5 vaccine vial using a sterile needle and syringe. For the purpose of this study one vial of reconstituted adjuvanted MCV-5 will be used for only one participant. 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. The single dose of 0.5 mL vaccine as per randomization schedule will be given via intramuscular injection using a needle and syringe in the deltoid muscle.

The compositions of a single 0.5 mL dose of reconstituted adjuvanted MCV-5 vaccine are:

Vaccine component	**Per 0.5 mL dose**
Meningococcal A polysaccharide*	5 μg
Meningococcal C polysaccharide#	5 μg
Meningococcal Y polysaccharide#	5 μg
Meningococcal W polysaccharide#	5 μg
Meningococcal X polysaccharide*	5 μg
Sucrose	2.42 mg
Sodium Citrate	0.40 mg
Tris (Trometomol)	0.098 mg
Al^{3+}adjuvant	125 μg
0.9% Sodium Chloride	q. s.
Tetanus Toxoid	7.8 to 33.4 μg
CRM	11.7 to 50.1 μg

*- Each conjugated to Tetanus Toxoid (TT);
- Each conjugated to CRM;
q.s. - Quantum satis

3.4.2. Non-Adjuvanted MCV-5

The non-adjuvanted MCV-5 is prepared by reconstituting one vial of MCV-5 with a 3.1 mL of 0.9% Sodium Chloride Injection, USP. For each participant, 0.5 mL dose will be withdrawn from the reconstituted five-dose non-adjuvanted MCV-5 vaccine vial using a sterile needle and syringe. For the purpose of this study one vial of reconstituted non-adjuvanted MCV-5 will be used for only one participant. 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. The single dose of 0.5 mL vaccine as per randomization schedule will be given via intramuscular injection using a needle and syringe in the deltoid muscle.

The compositions of a single 0.5 mL dose of reconstituted non-adjuvanted MCV-5 vaccine are:

Vaccine component	**Per 0.5 mL dose**
Meningococcal A polysaccharide*	5 μg
Meningococcal C polysaccharide#	5 μg
Meningococcal Y polysaccharide#	5 μg
Meningococcal W polysaccharide#	5 μg
Meningococcal X polysaccharide*	5 μg
Sucrose	2.42 mg
Sodium Citrate	0.40 mg
Tris (Trometomol)	0.098 mg
Tetanus Toxoid	7.8 to 33.4 μg
CRM	11.7 to 50.1 μg

* - Each conjugated to Tetanus Toxoid (TT);
# - Each conjugated to CRM;
q.s. - Quantum satis

3.4.3. Menactra®

After inspecting and confirming visually for particulate matter and discoloration 0.5 mL dose of vaccine is to be withdrawn from the single-dose vial using a sterile needle and syringe. The single dose of 0.5 mL vaccine as per randomization schedule will be given via intramuscular injection using a needle and syringe in the deltoid muscle. Vaccine must be administered within two hours of preparation.

3.5. Accountability and Disposal

Test vaccine MCV-5 and diluent used for reconstitution of adjuvanted formulation (sodium chloride plus aluminum phosphate) will be provided by SIIPL and shipped to the study site in validated cold chain boxes. The investigator will acknowledge receipt of products indicating shipment content and condition.

Whereas, site may arrange to directly procure Menactra® as well diluent for non-adjuvanted formulation (sodium chloride). In case it is not feasible for site, the same will be arranged by sponsor/designee**.**

The SIIPL supplied vaccine will be packed in appropriate package deemed to maintain the integrity of the product. The packaging for Menactra® will be the same as that available in market at the time of procurement.

Additional labels will be affixed on all study vaccines and diluents which should specify a statutory statement: '***Caution: New Drug--Limited by Federal law to investigational use***'.

The label should also have following details:

- Name of Manufacturer
- Protocol number
- Store between 2° and 8°C

A participant identifier will be captured or pre-printed on vaccine labels to ensure accountability and traceability to the study subject for which they were used.

All vaccines used in the study must be accounted for in the Vaccine Accountability Record.

Investigator or an authorized representative of the investigator will ensure that all vaccines will be stored in a secured area, in a light protected, dry place at temperature between +2°C and +8°C. Storage temperature should be monitored every day.

Qualified staff members will administer the vaccine.

The investigator must maintain a temperature log and an inventory record of vaccines received and administered.

At the end of the study, all vaccine will be destructed at the site, as per site's standard operating procedure or returned to SIIPL, including vaccine not administered to participants. It will be ensured that destruction occurs only after study product accountability.

4. STUDY POPULATION

4.1. Clinical Trial Site

This will be a single site study conducted at the Center for Vaccine Development (CVD), University of Maryland, Baltimore USA.

4.2. Study Population

Healthy adult volunteers, 18 to 45 years of age.

4.3. Eligibility

4.3.1. Inclusion Criteria

Male and female participants will be eligible for inclusion if ALL of the following apply at the time of screening:

1. Age 18 to 45 years of age inclusive
2. Written informed consent of volunteers
3. Healthy as established by medical history, laboratory evaluation and screening evaluations including clinical physical examination
4. Participants must have the following laboratory parameters:
    a. Hemoglobin: ≥ 10.5 g/dL for female, ≥ 11.0 g/dL for male
    b. White cell count: 3,300 to 12,000 cells/ mm3
    c. Platelets: 125,000 to 550,000/ mm3
    d. ALT < 1.25 times the institutional upper limit of normal (ULN)
    e. Creatinine and total bilirubin ≤ institutional ULN
    f. Albumin ≥ institutional lower limit of normal
5. Participants are able to understand and comply with planned study procedures and be available for all study visits
6. Female subjects must be of non-childbearing potential (defined as surgically sterile or postmenopausal for more than 1 year), or if of childbearing potential must be practicing abstinence or using an effective licensed method of birth control (e.g., history of hysterectomy or tubal ligation; use hormonal or barrier birth control such as implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), cervical sponges, diaphragms, condoms with spermicidal agents; or must have a vasectomized partner) within one month of vaccination and must agree to continue such precautions for 84 days after vaccination. A woman is eligible if she is monogamous with a vasectomized male.

4.3.2. Exclusion Criteria

Participants with any of the following criteria at study entry will not be eligible for participation:

1. Previous vaccination against *Neisseria meningitidis.*
2. Known exposure to *Neisseria meningitidis* in the past.
3. History of meningitis or seizures or any neurological or psychiatric disorder.
4. Administration of any other vaccine within 30 days prior or after administration of study vaccines.
5. Use of any investigational or non-registered drug or vaccine within 30 days prior to the administration of study vaccines or planned during the study.
6. History of allergic disease or known hypersensitivity to any component of the three study vaccines.
7. History of Serious Adverse Reactions following administration of Tetanus Toxoid, Diphtheria Toxoid or CRM containing vaccines.
8. History of Guillain-Barré syndrome.
9. Confirmed or suspected immunosuppressive or immune-deficient condition.
10. A family history of congenital or hereditary immunodeficiency.
11. Chronic administration (defined as more than 14 days) of immune-suppressants or other immune-modifying agents within six months prior to administration of study vaccine. (For corticosteroids, this means prednisone, or equivalent, > 0.5 mg/kg/day; topical or inhalable steroids are allowed.)
12. Laboratory confirmed infection of either hepatitis B virus (HBs Ag positive on ELISA), hepatitis C virus (anti-HCV positive on ELISA as well as PCR) or human immunodeficiency virus (HIV on ELISA).
13. Major congenital defects or serious chronic illness.
14. Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic, or renal functional abnormality, as determined by medical history, physical examination or laboratory screening tests.
15. Known bleeding disorders.
16. Administration of immunoglobulins and/or any blood products within the three months preceding the administration of study vaccines or planned administration during the vaccine period.
17. History (within the past year) or signs of alcohol or substance abuse.
18. Pregnancy or lactation. A negative pregnancy test will be required before vaccination for all women of childbearing potential.
19. A Body Mass Index (BMI) above 30.
20. Any other condition, which in the opinion of the investigator, might interfere with the study objectives, jeopardize the safety or rights of the participant or making it unlikely the participant could complete the protocol.

5. STUDY PROCEDURES

The study will be started only after the written approval from appropriate regulatory authority and the respective site's ethics committees are obtained.

The study Principal Investigator (PI) will ensure that the study team adheres to good clinical practices (GCP). Study personnel will be required to:

- Maintain control and retention of primary source documents and electronic databases with passwords, back-up, and restrict the ability to change results.
- Avoid coercive means of recruitment.
- Avoid excessive compensation that leads to the inclusion of participants who would otherwise be ineligible.
- Report adverse events and routine data to the external monitoring committee per the monitoring plan.
- Comply with the local regulatory and GCP requirements for vaccine-related adverse event reporting.
- Use infection control/biosafety measures to reduce exposure to infectious diseases, including during the transport of specimens.
- Report any anticipated changes to the protocol (such as randomization plan revisions) to the ethics committees and have approvals from such committees prior to initiating changes.

5.1. Recruitment

Participants may be recruited from the CVD volunteer database and by local advertisements and flyers. Potential participants who are interested in the study will be informed of the study and if they wish to participate, will receive additional study information, including the informed consent form.

5.2. Screening, Randomization, Masking Procedures, Study Visits

5.2.1. Initial and Continuing Informed Consent

Informed consent is the process of ensuring that study participants fully understand the purpose of the study and what will and may happen to them while participating in a research study. Initial written informed consent is required before performance of any study-related procedures. The informed consent process continues throughout the study. Key study concepts are reviewed with the participant at designated times and as needed, and the review is documented.

Additionally, if any new information becomes available that, in the judgment of the Sponsor and/or PI, may affect the participant's decision to continue in the trial, such information will be shared with the study participant and may be the basis for requiring a new consent form to be signed.

A copy of the signed informed consent form (ICF) will be provided to the participant and the original ICF will be filed with the participant's study record.

5.2.2. Screening, Visit 1 (Day -28 to -1)

Once informed consent has been obtained the participant will be considered enrolled in the trial. The following procedures will be completed during screening to determine study eligibility and may occur over multiple screening visits. Additional screening visits may be scheduled for any follow up as needed, but are not required. At the screening visit(s), the PI or designee will provide prospective volunteers with a detailed description of the study objectives and study participation requirements, as well as potential health risks and benefits associated with study participation. Baseline data are obtained during screening, which may occur over the course of several contacts/visits, between 28 days prior to and on Day 1, the day of vaccination. All inclusion/exclusion criteria must be assessed from data obtained within that period, unless otherwise specified in the eligibility criteria. After study information has been provided and the appropriate informed consent has been obtained, the following procedures are performed by PI/designee:

a) Confirms that written informed consent has been given and solicits and discusses any remaining questions the participant may have;
b) Assign screening number once study specific consent form has been signed;
c) Obtain demographic and contact (e.g., address, telephone, email) information;
d) Obtain medical history; including history of any vaccination in the last 30 days and ever received vaccination against *Neisseria meningitidis*, tetanus or diphtheria containing vaccines
e) Obtain history of medication use in the past 30 days;
f) Measure height & weight;
g) Perform full physical exam, including vital signs (blood pressure, pulse and temperature – section 5.5.1); and
h) Collect blood samples (18 mL) for screening laboratory testing: hematology (hemoglobin, platelet count and WBC), clinical chemistry (creatinine, albumin, ALT and total bilirubin), serum HCG pregnancy test (females of childbearing potential only) and screening for HIV, HCV and HBV (Appendix I).

5.2.3. Randomization

Enrollment will be performed online using the enrollment module of AdvantageEDC^{SM}, the Emmes Corporation's electronic data capture (EDC) system. Randomization will occur on the day participants are to receive their first study vaccination, after confirmation of eligibility and immediately prior to vaccination.

Participants will be assigned to a coded treatment assignment after demographic and eligibility data have been entered into the system. The unblinded pharmacist will be provided with the treatment assignment codes for preparation of the vaccine to be given to each participant. The research pharmacist will maintain the treatment code list in a secure place.

Based on this randomization schedule each participant will be assigned to one of the following three treatment groups:

Group	Vaccine
1	Adjuvanted Study vaccine (MCV-5)
2	Non-adjuvanted Study vaccine (MCV-5)
3	Reference vaccine (Menactra®, ACYW)

5.2.4. Vaccination, Visit 2 (Day 1)

Prior to Vaccine Administration

a) Obtain interim medical and medications history to confirm continued eligibility;
b) Measure vital signs;
c) Perform targeted physical exam based on complaints, interval history and to confirm absence of abnormality at the injection site (deltoid);
d) For female participants of child bearing potential, perform urine or serum pregnancy test;
e) Obtain blood samples (20 mL) for immunological testing; and
f) Record randomization code for eligible participant

Vaccine Administration

a) The prospective injection site will be cleaned with an alcohol swab and allowed to dry completely. The study injection will be administered into the deltoid by inserting the needle (25 gauge, 25 mm) into muscle at 90°, holding the muscle mass stable with the non-injecting hand, and slowly depressing the plunger. The needle is removed and the injection site gently rubbed with gauze.
b) An unblinded clinical staff not involved with clinical assessment will administer the assigned vaccine to the participant.
c) Document on the CRF as to timing and location of vaccine administration.

Post Dose – Observation Period

a) Participants will remain at the site for at least 60 minutes post-vaccination.
b) After 60 minutes study staff will assess and record oral temperature, systemic (headache, fatigue/malaise, myalgia, arthralgia, diarrhea and anorexia) and local injection site (pain, redness/erythema, swelling/induration) reactions.
c) The PI (or designee) may determine that a participant requires further on-site observation; or clinical assessments as needed.
d) When all study related procedures are complete and the PI (or designee) determines that a participant's condition is acceptable, the participant will be discharged from study site.
e) Before discharge, the participant will be provided with supplies including a thermometer, injection site measuring device, and a Memory Aid; instructed in their use; and provided with written materials, follow-up visit information, and contact telephone numbers for study staff.

5.2.5. Visit 3 (Day 8 +3 days)

On the eighth day after vaccination, the participant will return to the study site for the following procedures:

a) Study staff review and record participant's interim health history, medication use and self-assessment experience through personal interview, assisted by the Memory Aid.

b) Vital signs, injection site, and a targeted physical examination (if indicated) will be performed.

c) Local and systemic reactions and AEs review as recorded in Memory Aid as well as asked for by PI (or designee). The highest temperature written in the Memory Aid each day will be recorded to source document as peak temperature.

d) Findings of PI or study staff that suggest inaccuracy of reported self-assessments will be clearly documented.

e) Any topics or new information considered by PI to be important to continued informed consent will be shared with the participant.

f) Blood samples (8 mL) will be obtained for safety laboratory tests (Appendix I).

g) Study staff will instruct the participant regarding continued self-assessment and need to contact study staff (a) in follow-up of specific AEs, (b) if injection site changes worsen or do not resolve, (c) if systemic symptoms worsen or do not resolve, and (d) if other AEs occur.

h) The next visit is scheduled.

5.2.6. Visit 4 (Day 29 +14 days)

On Day 29 (plus 14 calendar days if necessary for participant compliance), the participant will return to study site and the following procedures occur:

a) Obtain interim medical history, including medication use.

b) Vital signs will be measured.

c) AEs will be evaluated.

d) A targeted physical exam will be performed, if indicated.

e) Urine pregnancy test will be performed.

f) Blood samples (30 mL) will be obtained for immunological assays (see Appendix I).

g) The participant will be reminded to contact the study site with any new information about chronic illnesses, serious health events, and/or hospitalizations, and the Day 85 follow-up contact information will be provided. Every effort should be made to adhere to the protocol windows.

5.2.7. Visit 5 (Day 85 +14 days)

On Day 85 (plus 14 calendar days if necessary for participant compliance), the participant will return to study site and the following procedures occur:

a) Interim medical history will be obtained, including medication use.
b) Vital signs will be measured.
c) SAEs, if any will be recorded and evaluated.
d) A targeted physical exam will be performed, if indicated.
e) Urine pregnancy test will be performed.

5.2.8. Final Study Contact (Day 180 ±21 days)

The participant will be contacted by telephone to assess any SAEs that may have occurred. SAEs, if any will be recorded and evaluated.

5.3. Unscheduled Visits

Unscheduled visits may be performed at participant's requests or directly by the study site when the PI or staff member considers it necessary for diagnosis and/or management of a finding or AE. All unscheduled visits will be documented in participants' study records and on applicable case report forms.

5.4. Early Termination

If a participant withdraws from the study for any reason prior to the planned study duration, every attempt is made to complete a termination visit to include the following.

a) Report of local and systemic reactogenicity and AEs are reviewed by PI (or designee).
b) Vital signs are obtained.
c) Specimens are obtained for chemistry, hematology and immunogenicity analysis if withdrawal occurs prior to schedule laboratory testing.
d) Memory Aid information is reviewed with the participant in detail by site staff, if in use since the last visit.
e) Injection site examination and a targeted physical examination are performed (if indicated).

5.5. Procedure Methods

Study procedures are performed and recorded in source documents as outlined in the Schedule of Events and according to the following subsections.

5.5.1. Vital Signs

- Temperature in degrees Fahrenheit (recorded to the nearest 0.1 degree) will be measured by oral thermometer.
- Blood pressure in mm of mercury and heart rate in beats per minute will be measured by automated device or manually.

5.5.2. Height and Weight

- Height will be measured in cm and recorded to the nearest 0.1 cm.
- Weight will be measured in kg and recorded to the nearest 0.1 kg.

5.5.3. Physical Examination

Full physical examination will include assessment of vital signs, head, eyes, ears, nose, oropharynx, neck, chest (auscultation), heart (auscultation), back, abdomen (auscultation and palpation), musculoskeletal, skin (especially injection site), and neurological. Not included are breast, genital or anorectal examinations.

5.5.4. Medical History

- A comprehensive medical history will be collected at screening including, history of any vaccination in the last 30 days and ever received vaccination against *Neisseria meningitidis*, tetanus and diphtheria containing vaccines, current medication and history of any chronic or recurrent medical and psychiatric conditions.
- An interim medical history will consist of inquiring regarding changes (healthcare events, signs, symptoms and changes in use of prescription or nonprescription drugs or herbal preparations) since the last medical history discussion.

5.5.5. Injection Site Examination

Injection site assessment will be done by trained study personnel. Local reactions will be graded according to the toxicity grading scale in Appendix II.

- Erythema/redness will be examined under standardized lighting conditions and measured. Severity of the reaction will be determined by staff on the basis of the severity grading table (Appendix II).
- Swelling/induration will be examined by palpation and visual inspection under standardized lighting conditions; the examiner may temporarily mark skin at margins of visible swelling/induration, then measure maximum diameter (as per Appendix II).
- Pain will be assessed by (a) inquiring as to whether there is significant discomfort at rest and/or (b) whether movement of the injection site causes discomfort, impacts limb movement or daily activity (Appendix II).

5.5.6. Assessment of Reactogenicity

The following parameters for reactogenicity will be assessed during the seven days following vaccination.

Local reactogenicity

- Pain
- Erythema / redness
- Swelling / induration

Systemic reactogenicity

- Fever (based on oral temperature)
- Headache
- Fatigue/malaise
- Joint pain (arthralgia)
- Muscle pain (myalgia)
- Diarrhea
- Anorexia
- Chills
- Vomiting

5.5.7. Concomitant Therapy

Other medications that are considered necessary for participant's welfare and that will not interfere with the vaccine may be given at the discretion of the investigator. At each study visit, the investigator/designee should ask the participants about concomitant medication.

Any of the medication taken at any time during the period starting 30 days before the first study vaccination and ending four weeks after the final study vaccination must be captured with trade name and/or generic name, indication, start and end dates.

The following drug/vaccines should not be taken during study participation:

1. Any investigational or non-registered drug or vaccine within 30 days prior to administration of study vaccines as well as during the entire study participation.
2. Chronic administration (defined as more than 14 days) of immunosuppressant or other immune-modifying agents during the vaccine period. For corticosteroids, this means prednisone or equivalent $\geq$ 0.5 mg/kg/day. Topical or inhalable steroids will be allowed.
3. Administration of routinely recommended licensed vaccine within 28 days post vaccination.
4. Administration of immunoglobulin and/or any blood products during the study period.
5. Prophylactic antipyretics or analgesics to prevent fever or pain for seven days post vaccination.

5.5.8. Clinical Laboratory Testing

Laboratory evaluations for screening (hematology, chemistry, testing for HIV, Hepatitis B and C, and, for women of childbearing potential, pregnancy tests) and safety monitoring (hematology, chemistry and pregnancy tests for women of child bearing potential) are detailed in Appendix I, Schedule of Events.

5.5.9. Early Termination from Study

An enrolled/vaccinated participant may be terminated from the study for any of these reasons:

a) Participant withdraws consent.
b) The participant fails to comply with the study requirements so as to cause harm to him/herself or seriously interfere with the validity of the study results.
c) Sponsor terminates the study.

5.5.10. Contraception and Pregnancy

Contraception status is assessed and documented prior to enrollment and study vaccination for female participants who are of childbearing potential. Prior to enrollment and at vaccination visit, staff will ask participants to verbally confirm their use of adequate contraception methods if they are able to become pregnant. Adequate methods of contraception include double barrier contraception, hormonal birth control, IUD, or surgical sterility. If a participant becomes pregnant following vaccination, she will be encouraged to complete remaining visits and study procedures unless medically contraindicated. Any participant who becomes pregnant during the period between first vaccination and Day 180 will continue to be followed for pregnancy outcome, if possible.

6. LABORATORY EVALUATIONS

Blood samples will be obtained to examine vaccine safety and immunogenicity.

6.1. Sample Collection, Distribution and Storage

Samples to evaluate vaccine safety will be obtained at the clinical trial site and transported to the site's designated laboratory for clinical testing. Research specimens collected for the immunogenicity time points will be separated into aliquots by the site's research laboratory or study laboratory as per study specific process and sent to the contract laboratories. Samples will be stored properly in controlled-temperature refrigerators/freezers. Backup generators are available for proper sample storage.

6.2. Safety Clinical Laboratory Assays

Protocol mandated screening and clinical safety laboratory tests will be conducted in real time as per Schedule of Events (Appendix I).The clinical laboratory must maintain proper accreditation and subscribes to a proficiency testing program.

Laboratory results will be reviewed promptly by the PI or designee. Participants will be notified of any clinically significant abnormalities. If clinically significant abnormalities are identified during screening, participants will be referred to their primary health provider or appropriate medical center. If identified during the study, participants may be asked to return to the study site for further evaluation, including clinical evaluation and repeat laboratory testing as warranted.

6.3. Immunological Assays

The immunological assays to be performed are:

Immunogenicity testing for Meningococcal Polysaccharide A, C, Y, W, and X specific antibodies using rSBA assay will be performed on sera collected at baseline (Day 1) and 28 days post vaccination. The rSBA assay will be conducted at Vaccine Evaluation Unit at Public Health England (PHE) in Manchester UK. Additional immunogenicity assays may be performed by research laboratories to further evaluate post-vaccination immune responses. These exploratory analyses may be done on a sub-sample of participants' sera, if remaining specimen volume is adequate.

6.4. Assay Qualification, Standardization and Validation

The PHE rSBA assay for serogroups A, C, Y, and W is a validated assay. Samples from this study will be used for the validation of the PHE rSBA assay for serogroup X.

6.5. Biohazard Containment

As transmission of blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as recommended by the Centers for Diseases Control and Prevent (CDC). All biological specimens will be transported using packaging mandated by 42 CFR Part 72. All dangerous goods materials, including diagnostic specimens and infectious substances, must be transported according to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations.

Biohazardous waste will be contained according to institutional, transportation/carrier, and all other applicable regulations.

7. STATISTICAL DESIGN AND ANALYSIS

7.1. Overview and General Design

This study is a Phase 1 double blinded randomized, controlled clinical trial to assess the safety and immunogenicity of the adjuvanted and non-adjuvanted formulation of polyvalent conjugate vaccine composed of serogroups A, C, Y, W, and X *Neisseria meningitidis* capsular polysaccharides (MCV-5). The primary objective is to evaluate the safety of adjuvanted and non-adjuvanted formulations of MCV-5 vaccine. The secondary objective is to assess the immune response of adjuvanted and non-adjuvanted formulations of MCV-5 vaccine.

The primary hypothesis of safety will be fulfilled if no participants develop a vaccine related SAE and the vaccine is well tolerated. The second hypothesis of immunogenicity will be fulfilled if the two formulations of MCV-5 induce immune response as measured by rSBA to all five serogroups of the vaccines.

A detailed statistical analysis plan for preparation of the final study report will be created and made final prior to database lock and unblinding. All statistical analyses will be performed using SAS® software Version 9.3 or later.

Medical history and AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The frequency count and percentage of participants will be summarized according to the coded terms of system organ class and preferred term. Participant-wise data listing will be provided.

7.2. Randomization and Blinding Procedures

The randomization scheme will be generated and maintained by the Statistical and Data Management Group (SDMG) at the Emmes Corporation, Rockville, MD. Participants will be enrolled into the study online and randomized using the enrollment module of the Emmes Corporation's AdvantageEDC℠ electronic data capture system. Each participant enrolled into the trial will be assigned a treatment code after demographic and eligibility data have been entered into the system.

The pharmacist with primary responsibility for dispensing study products is charged with maintaining security of the treatment assignments.

7.3. Objectives and Endpoints

7.3.1. Primary

Objective: To evaluate the safety of adjuvanted and non-adjuvanted formulations of MCV-5 vaccine in healthy adults.

Endpoints:

Summaries by product received including the number and percentage of participants experiencing:

- immediate AEs within 60 minutes post-vaccination;
- solicited local or systemic post vaccination reactogenicity reactions within seven days following vaccination (Days one through seven);
- any SAE within six months following vaccination;
- any AE within 28 days following vaccination;
- any Grade 2 or greater solicited local or systemic post vaccination reactions within seven days following vaccination;
- any Grade 2 or greater unsolicited AE within 28 days following vaccination;
- any unsolicited AE within 28 days following vaccination judged to be related to study product; and
- any Grade 2 or greater unsolicited AE within 28 days following vaccination judged to be related to study product.

7.3.2. Secondary

Objective: To assess the immune response of adjuvanted and non-adjuvanted formulations of MCV-5 vaccine in healthy adults

Endpoints:

- The percentage of participants who show a seroconversion for Meningococcal Polysaccharide A, C, Y, W, and X specific antibodies, i.e. a ≥4-fold increase in post-immunization rSBA titer with respect to pre-immunization rSBA titer, at 28 days after a single vaccine dose.
- The percentage of participants who show a post-immunization seroprotection titer for Meningococcal Polysaccharide A, C, Y, W, and X specific antibodies defined as rSBA titer of 1:8 and 1:128 at 28 days after a single vaccine dose.
- GMTs of Meningococcal Polysaccharide A, C, Y, W and X specific antibodies at 28 days after a single vaccine dose, as measured by rSBA assay.

7.3.3. Exploratory

Immune response of adjuvanted and non-adjuvanted formulations of MCV-5 may be assessed by other relevant assays, if remaining specimen volume is adequate.

7.4. Sample Size Justification

Since this study is a Phase 1 trial it is designed to provide preliminary safety and immunogenicity data that may support testing the study product in additional larger cohorts in adults and in age-descending studies.

With 20 vaccine recipients per vaccine group, this study's design allows a greater than 90% chance of observing an AE that has an 11% chance of occurrence. Conversely, if no AEs are observed in 20 vaccine recipients, the study will be able to rule out AEs occurring at a rate of approximately 14% based on the upper bounds of the one-sided 95% Confidence Interval.

No formal statistical hypothesis testing is planned for this first time in human Phase 1 study whose objectives are aimed to descriptively evaluate the safety and immunogenicity profile of the study vaccines

7.5. Analytical Methodology

7.5.1. Analysis Population

Definitions of analysis populations to be analyzed are:

Enrolled Population

All screened participants who provide informed consent, regardless of the participant's randomization and treatment status in the trial.

Full Analysis population

All participants in the enrolled population who were randomized and received a study vaccination. All safety analyses will be performed using this population. Treatment groups for safety analysis will be assigned according to the actual treatment received at Day 1.

Per Protocol population

All participants in the per protocol population who are assigned the study vaccination with no major protocol violations that are determined to potentially interfere with the immunogenicity assessment of the study vaccine. This population will serve as the primary analysis population for the immunogenicity endpoints.

The criteria for exclusion of participants from the Per Protocol Population will be established before breaking the blind and will be based on the blinded review of protocol violations.

7.5.2. Statistical Method

When the use of descriptive statistics to assess group characteristics or differences is required, the following methods will be used: for categorical variables, the number and percent of participants in each category; for continuous variables, the mean, median, standard deviation, quartiles and range (minimum, maximum).

In general all missing data will be treated as missing completely at random and no imputation will be performed except for the safety endpoints as described below. Non-analyzable data (e.g., due to major protocol violations) will be documented in the deviations.

If some safety data are available for a subject in the safety population but respective secondary endpoint related data are missing then the subject will be included in the safety analysis and data will be treated as follows for immediate AEs, solicited AEs, unsolicited AEs and SAEs.

1. If Severity is missing for any AE then it will be considered as an AE of maximum severity (Grade 3) “Severe” unless it’s captured as SAE.
2. If “Relationship” is missing then it will be considered as “Related” to the vaccine administered.
3. If, for Start date, the day of event/condition is missing due to any adverse event then it will be imputed as the date of last dose of study vaccine.
4. If, for Start date, the day and month of an adverse event is missing, then it will be imputed as the date of first dose of study vaccine.
5. If the Stop date of an adverse event is missing then it will be treated as ongoing.

Analysis of Primary Safety Objective

The primary aim of the study is to assess the safety of the study vaccine. All safety data (solicited local and systemic reactions and unsolicited AEs and SAEs) collected after participants are exposed to the study product will be included in the primary analysis of safety.

To assess safety, the number and percentage of participants experiencing at least one AE, and the number and percentage of participants experiencing each specific AE, categorized by body system and preferred term, will be tabulated by product received along with their corresponding two-sided exact 95% confidence intervals.

Fisher’s exact test will be used to compare the proportion of participants with solicited local and systemic reactogenicity events between the MCV-5 group and the Menactra® Group. The primary purpose of statistical comparisons is to screen out potential solicited reactogenicity events that need further clinical evaluation. Therefore, they are not considered formal statistical hypothesis tests and it is acknowledged that there will be inflated Type I errors (i.e. inflated false statistical significances) from performing multiple unadjusted comparisons.

Changes in clinical laboratory values from baseline to end of treatment/follow-up will be analyzed descriptively.

To facilitate the planning of the follow-up trial, analysis of unblinded primary safety data up to Visit 4 (Day 29) by treatment groups will be made available to the Sponsor after all participants have completed this visit and their data have been cleaned and verified.

Analysis of Secondary and Exploratory Immunogenicity Objective

The percentage of participants with a 4-fold response in rSBA titer against serogroups A, C, W, Y and X will be defined as:

- For participants with a pre-vaccination rSBA titer <8, a post-vaccination titer of ≥32;
- For participants with a pre-vaccination rSBA titer ≥8, an increase in rSBA titer of at least 4 times the pre-vaccination titer.

For seroresponse rate endpoints, two-sided 95% exact confidence intervals (CIs) for each of the proportions will be provided. Two-sided exact 95% CIs for the three pair-wise proportion differences between the three treatment groups will be computed using the unconditional exact method proposed by Chan and Zhang (1999) or another appropriate method.

For the purpose of determining GMT antibody titer below 1:8 will be given an arbitrary value of half of the assay's cut-off (4). GMT will be calculated as: GMT = antilog (mean loge-x]) where x is the assay result and e is the natural logarithm. GMTs will be summarized by treatment group and by visit with corresponding two-sided 95% CIs based on the t-distribution to provide population estimates. Two-sided 95% CIs for the ratios of GMTs between treatment groups will be constructed using the log normal distribution. The log values will be used to construct a CI using the t-distribution for the mean difference between three pair-wise treatment groups. The mean difference and the corresponding CI limits will then be exponentiated to obtain the GMT ratio and the corresponding CI. If the values deviate from a log normal distribution, a nonparametric method may be used for the analysis of GMT.

Due to the hypothesis generating nature of multiple statistical comparisons for immunogenicity associated with multiple endpoints for this early phase first study in human subjects, all estimations will be carried out using a two-sided 5% Type I error rate without an adjustment for multiple comparisons.

8. SAFETY ASSESSMENT AND REPORTING

This section defines the types of safety events that should be reported and outlines the procedures for appropriately collecting, grading, recording and reporting them.

8.1. Safety Events

All safety events observed under this protocol are reported through the AdvantageEDC data system throughout the study. Safety events related to vaccine reactogenicity are collected on study-specific forms. Reactogenicity will be collected through the visit on Day 7, if a solicited sign or symptom has started during the seven days post-vaccination and continues it will continue to be reported as a reactogenicity symptom. Only when the reactogenicity event is considered an SAE, as defined below, will it be reported on an AE/SAE form set, in addition to the reactogenicity form. Any symptom starting after seven days post-vaccination will be recorded as an AE. All other

safety events that meet the definition of an AE or SAE that occur throughout the study are reported on the AE/ SAE form set. AE's will be collected through study visit Day 28. SAEs will be assessed through Day 180 and will be reported on the AE/ SAE form set.

8.2. Reporting Period

Safety events are reported from the time of the vaccination through completion of the study at 6 months as described above.

8.3. Definitions

8.3.1. Adverse Event (AE)

An adverse event is any untoward medical occurrence in humans, whether or not considered vaccine related, that occurs after the vaccination during the conduct of a clinical trial. Any change from baseline assessment of clinical status, ECGs, routine laboratory tests, X-rays, physical examinations, etc., that is considered clinically significant by the PI is considered an AE.

Suspected adverse drug reaction is any AE for which there is a reasonable possibility that the vaccine caused the AE. A reasonable possibility implies that there is evidence to suggest that the study product caused the event.

Adverse reaction is any AE caused by the vaccine.

8.3.2. Serious Adverse Events (Defined as Serious Adverse Events, Serious Suspected Adverse Reactions or Serious Adverse Reactions)

An SAE, including a serious suspected adverse reaction or serious adverse reaction as determined by the PI or the Sponsor, is any event that results in any of the following outcomes:

1. Death.
2. Life-threatening AE (Life-threatening means that the study participant was, in the opinion of the PI or Sponsor, at immediate risk of death from the event as it occurred.)
3. Inpatient hospitalization or prolongation of existing hospitalization.
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5. Congenital abnormality or birth defect.
6. Important medical event that may not result in one of the above outcomes but may jeopardize the health of the study participant or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event.

8.3.3. Unexpected Adverse Event

An AE is “unexpected” when its nature (specificity) or severity is not consistent with applicable product information, such as safety information provided in the Investigators’ Brochure (IB), the investigational plan or the protocol.

8.4. Severity Grading

The study site assigns severity grades to indicate the severity of adverse events and reactions. The severity grading criteria provided in Appendix II grade AEs from Mild (Grade 1) to Life Threatening (Grade 4). All AEs leading to death are Grade 5 events. AEs are graded with the worst severity grade during the illness/symptoms. AE severity will be graded using the attached grading scale (Appendix II) based on the *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events*, version 2.0, November 2014, of the US National Institute of Health.

8.5. Guidelines for Determining Causality of an Adverse Event

The PI should consider the following question when assessing causality of an AE to study product:

Is there a reasonable possibility that the study product caused the event?

Reasonable possibility implies there is evidence to suggest that the study product caused the reported event. An affirmative answer designates the event as a suspected adverse reaction, and the AE is considered “related”. If the answer is no, then the AE is considered “unrelated”.

The causality assessment is made on the basis of the available information at the reporting time point. Assessment of causality can change according to follow-up information.

8.6. Assessment of Outcome of Adverse Event

The outcome of adverse event will be assessed as at the time of last observation as per the following categories:

- Recovered/resolved without sequelae
- Recovered/resolved with sequelae
- Ongoing at the end of the study
- Death
- Unknown. The outcome of the AE is not known

8.7. Adverse Event Identification, Resolution and Reporting

To improve the quality and precision of acquired AE data, the PI should observe the following guidelines:

- Whenever possible, use recognized medical terms when recording AEs on the AE CRF. Do not use colloquialisms and/or abbreviations.
- If known, record the diagnosis (i.e., disease or syndrome) rather than component signs, symptoms and laboratory values on the AE CRF (e.g., record congestive heart failure rather than dyspnea, rales, and cyanosis). However, signs and symptoms that are considered unrelated to an encountered syndrome or disease should be recorded as individual AEs on the CRF (e.g., if congestive heart failure and severe headache are observed at the same time, each event should be recorded as an individual AE).

- AEs occurring secondary to other events (e.g., sequelae) should be identified by the primary cause. A “primary” AE, if clearly identifiable, generally represents the most accurate clinical term to record on the AE CRF. If a primary serious AE (SAE) is recorded on an SAE CRF, events occurring secondary to the primary event should be described in the narrative description of the case.

  For example:

Orthostatic hypotension	→	Fainting and fall to floor	→	Head trauma	→	Neck pain

  The primary AE is orthostatic hypotension.

- Grade 2 or higher abnormal laboratory test results will be reported as AEs and assessed for severity according to severity grading criteria provided in Appendix II and causality (related or unrelated) to the study product. Grade 1 abnormal laboratory test results will be entered as AEs if the site PI determines them to be clinically significant.
- Death is an outcome of an event. The event that resulted in the death should be recorded and reported on the SAE CRF.
- For hospitalizations for surgical or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the case narrative as part of the action taken in response to the illness.
- Pregnancies that occur in study participants are not considered AEs and will be recorded on a separate Pregnancy CRF. Pregnancy outcomes that include stillbirth and any congenital anomalies must be reported as SAEs.

AEs may be discovered through any of these methods.

- Observing the participant.
- Questioning the participant, which should be done in an objective manner.
- Receiving an unsolicited complaint from the participant.
- Review of medical records/source documents.

Each participant will have a scheduled observation following vaccination, including a symptom-directed physical examination, if indicated. They will be monitored in-house for 60 minutes after vaccination. On Days 1 to 7 after vaccination, participants will be instructed to assess and record daily in a participant memory aid any signs and symptoms at the injection site, as well as systemic signs and symptoms. Follow-up visits will be conducted seven days after vaccination, including directed assessment, safety tests and verification of memory aid notes. They will be instructed to call the study team if they observe significant injection site or systemic signs or symptoms, and then to continue monitoring and reporting their condition. All participants will be followed for safety for six months after the vaccination.

8.7.1. AE Resolution

All reported AEs should be followed until resolution or stabilization, or until the participant's participation in the study ends. Participants who have an ongoing study product-related SAE at study completion or at discontinuation from the study will be followed by the PI or his designee until the event is resolved or determined to be irreversible, chronic, or stable by the PI.

8.7.2. General Recording and Reporting Procedures

A multi-page AE/SAE form set will be used allowing all AEs to be submitted through a single reporting mechanism. SAEs will require additional information reported on additional pages within the Internet data entry system. As appropriate or per request of the Emmes medical monitor or Sponsor medical officer, source documents (e.g., hospitalization discharge summaries) may be uploaded to the AE/SAE form set as well. The PI will treat or refer, as appropriate, participants experiencing AEs and observe them at suitable intervals until their symptoms resolve or their status stabilizes.

8.7.3. SAE Recording and Reporting Procedures

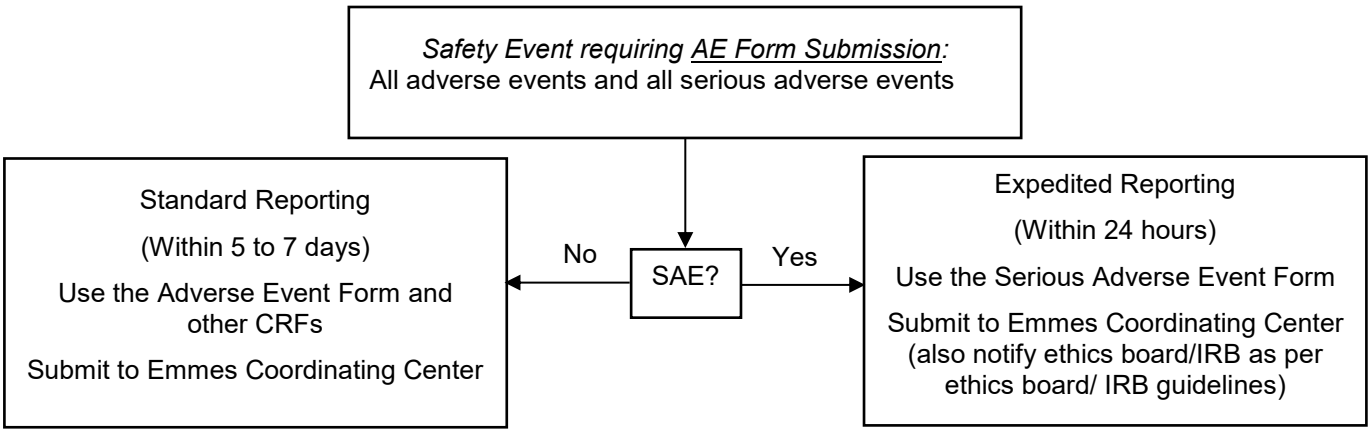
SAEs will be recorded on the AE CRF. The site is obligated to report SAEs to the Emmes Coordinating Center within 24 hours of the site's knowledge of the event. The Emmes Coordinating Center will in turn pass on that information to Sponsor and SIIPL.

The following attributes will be assigned by the PI or assignment by designee will undergo documented review by the PI:

- Description
- Date of onset and resolution (if known when reported)
- Severity
- Assessment of relatedness to test article
- Action taken

8.7.4. Site Reporting of Events

Figure 3: Reporting Decisions for Adverse Events



- Notify the PI.
- Complete and transmit an AE Form through the Internet data entry system. Information regarding a SAE report must be recorded in the participant's medical chart and entered in the Internet data entry system.
- SAE follow-up reports should include hospital admittance notes, hospital discharge summary, clinical notes, resolution date, treatment, and any other pertinent information regarding the event. If not immediately available, reporting should not be delayed to provide these documents.
- In the event of a death, the SAE Form must be completed and transmitted along with other supporting data (e.g., death certificate, medical notes).

8.8. Serious Adverse Event Notification

8.8.1. Notifications and Review

The PI will provide the Emmes Coordinating Center with data for all SAEs, as defined per the protocol, on a timely manner by entering the information in AdvantageEDC. The Emmes Coordinating Center is responsible for notifying the Sponsor and will do so simultaneously with the reporting to the clinical database. Notification of reported events will be generated at the time of entry into the data system, and all SAEs will be reviewed promptly by the Emmes medical monitor within the data system. As noted above, this notification should be within 24 hours of site awareness of the event. Site personnel will be trained in reporting AEs and SAEs.

The Emmes medical monitor will review all unanticipated events involving risk to participants or others, SAEs and all participant deaths associated with the protocol and will provide a written report. At a minimum, the Emmes medical monitor must comment on the outcomes of the event or problem and, in case of an SAE or death, comment on the relationship to participation in the study. The Emmes medical monitor must also indicate whether he/she concurs with the details of the report provided by the PI.

Summary review of all reported AEs and SAEs will be compiled on a weekly basis to identify any safety trends. Review of safety laboratory tests will also be conducted on a weekly basis.

8.8.2. Expedited Reporting

The Emmes Coordinating Center will be responsible for expedited IND Safety Reports and IND Annual reports to the FDA.

When expedited reports as defined below are required, the cover memorandum, MedWatch Form FDA 3500A, and any pertinent attachments will be processed by the Emmes medical monitor and a copy of the completed report will be submitted by fax or courier delivery before the regulatory reporting deadline, to the following persons:

- FDA medical officer as appropriate (submitted as an amendment to the applicable IND)
- PI (who is responsible for forwarding the report to the local/central IRB)
- Safety Review Committee members

If relevant follow-up information becomes available, the Emmes medical monitor will be responsible for obtaining and reviewing details from the site. A follow-up MedWatch form will be completed and forwarded to all parties that received the earlier SAE report. A copy of the safety sections for annual FDA reports will be forwarded to PATH.

Suspected adverse reactions that are serious and unexpected will be reported to the FDA within 15 days, or for deaths and life threatening events that are both suspected adverse reactions and unexpected, within 7 days (per 21 CFR 312.32). The IND Safety Report will be unblinded to treatment allocation and determination of relationship to study product based on the assessment of the sponsor.

Subsequent review by the FDA, the SRC, IRB, or the Sponsor may suspend further study product administration or procedures. The FDA and the study Sponsor with consultation with the SRC retain the authority to suspend additional enrollment for the entire study as applicable.

8.8.3. Notifying the Safety Review Committee

The Emmes Coordinating Center will provide the SRC with listings of all SAEs on an ongoing basis. Furthermore, the SRC will be informed of expedited reports of SAEs.

8.8.4. Notifying the Institutional Review Board

The PI will ensure the timely dissemination of required AE information, including expedited reports, to the IRB in accordance with applicable local regulations and guidelines. The PI is responsible for submitting the IND Safety Report (initial and follow up SAE reports) or other safety information (e.g., revised IB) to the site's IRB and for retaining a copy in the site's study file.

University of Maryland, Baltimore (UMB) IRB

Using the same criteria above, any qualifying SAE will be reported to the UMB IRB, as a reportable new information event and within five business days. The contact information for the UMB IRB is as follows:

University of Maryland, Baltimore
Human Research Protections Office
Lexington Building
620 West Lexington Street, Second Floor
Baltimore, MD 21201
410-706-5037

9. SAFETY MONITORING

Extensive safety monitoring will be provided for this protocol. The PI and/or designated site staff will be responsible for continuous close safety monitoring of all study participants and for alerting the Sponsor if unexpected concerns arise or pause criteria are met.

9.1. Safety Review Committee

A Safety Review Committee, comprised of the PI, a medical expert with experience in vaccine pharmacovigilance not involved with the study, the Emmes medical monitor, SIIPL and PATH medical officer will monitor safety throughout the duration of the study. The Emmes study statistician with assistance of the data management staff will prepare safety reports as needed for SRC discussions. During the vaccination period the SRC will review weekly the safety data. At any time during the study, the Emmes Coordinating Center will notify the SRC of ad hoc review if pause criteria may have been met. The SRC reviews will be summarized with consensus recommendations to the study Sponsor as to whether there are safety concerns and whether the study should continue without change, be modified, or be stopped. The SRC may request review of unblinded safety data by the pharmacovigilance expert in its deliberation. SRC consensus recommendations regarding modifying or stopping further enrolment may involve Sponsor consultation with the local regulatory authority.

The SRC members must be satisfied that the timelines, completeness, and accuracy of the data submitted to them for review are sufficient. Items reviewed by the SRC may include: study participant demographic information; interim/cumulative data for evidence of study-related AEs; data quality, completeness, and timeliness; and factors external to the study, such as scientific or therapeutic developments that may impact participant safety or the ethics of the study. If at any time, a decision is made to discontinue administration of study product in all participants, expeditious notification will be provided by the sponsor to the US FDA and by the PI to the site IRB.

9.2. Study Pause Rule

The following study pause rules will automatically pause or halt further vaccinations. However participants already enrolled will continued to be followed for safety during the pause. These pause rules refer to suspected adverse reactions and will be triggered automatically if any of the event described below are met during the conduct of the study:

- One or more participants experience a serious adverse reaction.
- One or more participants experience a Grade 4 injection site reaction.
- Two or more participants experience the same Grade 3 injection site reaction.
- Two or more participants with the same severe (Grade 3) systemic reactogenicity signs or symptoms, within seven days following vaccination.
- Two or more participants experience the same vaccine-related Grade 3 or higher clinical (including fever) or laboratory abnormality.

9.2.1. Pause Procedure

- The SRC will be notified by the Emmes Coordinating Center and convene ad hoc review if pause criteria may have been met.
- At scheduled study review, the SRC may also identify adverse events that could potentially qualify as pause criteria.
- If the PI (or designee), the Emmes medical monitor or any member of the SRC identifies that a pause criterion may have been met or propose the study be paused on a discretionary basis, all vaccinations and enrollment will be suspended. The SRC will be notified and will expeditiously (within 48 hours) convene to review all available, relevant information. The SRC may request review of unblinded safety data by the pharmacovigilance expert, The SRC reviews will be summarized with consensus recommendations to the study Sponsor as to whether there are safety concerns and whether the study should continue without change, be modified, or be stopped.
- If at any time, a decision is made to discontinue administration of study product in all participants, expeditious notification will be provided by the Sponsor to the US FDA and by the PI to the IRB within 48 hours.
- If the Sponsor re-starts the study after SRC review and recommendation, enrollment and vaccination may resume.

10. DATA MANAGEMENT

The PI is responsible for ensuring the accuracy, completeness, and timeliness of the data reported. Data collection is the responsibility of the clinical trial staff at the study site under the supervision of the study PI. The Emmes Corporation is responsible for data management activities, including quality review, analysis, and reporting of the study data according to Standard Operations Procedure (SOP).

10.1. Case Report Form Development and Completion

Electronic Data Capture will be the method of data collection in this study. The electronic Case Report Forms (eCRFs) will be developed by the Emmes Corporation and approved by SIIPL and PATH. Clinical data (including AEs, concomitant medications, and reactogenicity data) and clinical laboratory data will be entered into the 21 CFR Part 11-compliant Internet Data Entry System (IDES) provided by The Emmes Corporation. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

Data for each participant will be recorded in the eCRF. It is the PI's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported in the participant's eCRF and any supporting documentation. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Source documentation supporting the eCRF data should indicate the participant's participation in the study and should document the dates and details of study procedures, AEs and the participant's status. The PI/institution will maintain all information in the eCRFs and all source documents that support the data collected from each participant.

The PI or designated representative should complete the eCRFs as soon as possible but within three days after information is collected. Completed eCRFs must be submitted for each screened participant who signs the study-specific ICF. The eCRFs will not be completed for participants who do not sign the study specific ICF. The PI will retain all essential documents.

10.2. Details of Data Management

A Data Management Handbook (DMH) will be written by The Emmes Corporation and contain all study-specific requirements.

10.2.1. Coding

The PI is responsible for ensuring the accuracy, completeness, and timeliness of the data reported. Data collection is the responsibility of the clinical trial staff at the study site under the supervision of the study PI. The Emmes Corporation is responsible for data management activities, including quality review, analysis, and reporting of the study data according to SOPs.

10.2.2. Data Validation

The Emmes Corporation will inspect the data entered into the database for completeness and consistency.

10.2.3. Source Data Verification

For source data verification (SDV), the monitor (on behalf of the study Sponsor) must have direct access to source documents that support the data recorded, e.g., medical records, original laboratory records and ICFs. If source data are electronic, these data must be printed, signed and dated by the PI and stored in the participant's study file. Clinical laboratory data will remain in study participant records. Essential documents, including ICFs, must be filed and kept in the study files on an ongoing basis.

10.2.4. Definition of Source Data

Source data are all information in original records or certified copies of original records of clinical findings, observations, or other activities in a clinical study. Source data are contained in source documents.

10.2.5. Definition of Source Document

Original source documents include data and records, e.g., hospital records, medical notes, laboratory notes, evaluation checklists, pharmacy dispensing records, records kept at the pharmacy and at the laboratory, documentation of shipments. Note that, for this protocol, the volunteer participant data collection tool (i.e., the Memory Aid) is not considered a source document. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained.

10.3. Database Locking Procedures

- A final database lock for the primary analysis will occur after all participants have completed all follow-up visits, a case-by-case review of the severity of any AEs has been performed and finalized, all data anomalies have been resolved and monitoring is complete.
- Remaining immunology data will be maintained in a separate immunology database.

10.4. Record Archival

The PI is responsible for retaining study records for a period of two years following the date that a marketing application is approved for the product or, if no application is to be filed or, if a file application is not approved, until two years after the investigation is discontinued and the FDA is notified. The Sponsor will be responsible for providing the site with date of vaccine approval or IND withdrawal.

These records are also to be maintained in compliance with IRB, state, and federal medical records retention requirements, whichever is longest. Storage of all trial-related documents will be such that confidentiality will be strictly maintained to the extent provided by federal, state, and local law.

10.5. Screen Failures

If a participant signs the study-specific ICF, but is not randomized because of non-eligibility (a screen failure), the reason for his/her non-eligibility should be entered in the medical records/notes/charts. Also, a screening log must be kept. Data from participants who fail screening will not be recorded in the eCRF, with the exception of demographic data and the reason for screen fail.

10.6. Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or site SOP requirements. The noncompliance may be either on the part of the participant, the PI, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- Compliance with Protocol, Sections 4.5.1, 4.5.2, and 4.5.3.
- Quality Assurance and Quality Control, Section 5.1.1.
- Noncompliance, Sections 5.20.1 and 5.20.2.

It is the responsibility of the site to exercise continuous vigilance to identify and report deviations within five working days after identification of the protocol deviation, or within five working days of the scheduled protocol-required activity. All deviations must be promptly reported to Emmes and sponsor via the appropriate eCRF within the electronic data system.

All deviations from the protocol must be addressed in study participant source documents. Protocol deviations must be sent to UMB IRB per its guidelines. The site PI/study staff is responsible for knowing and adhering to UMB IRB's requirements.

11. STUDY MONITORING

Sponsor monitoring responsibilities will be provided by The Emmes Corporation. A site initiation visit will be conducted prior to beginning the study, and monitoring will be conducted at initiation, during, and at closeout of the study by the study monitor or designee.

During the course of the study, the Emmes monitor will visit the clinical site at intervals to verify compliance to the protocol; check for completeness, accuracy, and consistency of the data and study product accountability; adherence to CFR, and any additional regulations and requirements, including GCP, of the conduct of clinical research. The monitor should have access to participant medical records, study product accountability and other study-related records needed to verify the entries on the eCRFs.

The PI and the monitor must agree to cooperate to ensure that any problems detected in the course of these monitoring visits, including eCRF completion and query resolution, are resolved in a predefined timeframe.

To ensure the quality of clinical data across all participants at the site, a clinical data management review will be performed on volunteer data received at The Emmes Corporation. During this review, participant data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications will be sent to the site for resolution prior to the site's last monitoring close-out visit.

Essential documents must be filed in the site study file on an ongoing basis and available for review by the Emmes monitor. Monitoring visits will be performed according to the Clinical Monitoring Plan.

11.1. Independent Auditing

The SIIPL or PATH representatives may audit the study to ensure that study procedures and data collected comply with the protocol and applicable SOPs at the clinical site and The Emmes Corporation, and that data are correct and complete. The PI will permit auditors (employees of the Sponsor or an external company designated by the Sponsor) to verify source data validation of the regularly monitored clinical study. The auditors will compare the entries in the eCRFs with the source data and evaluate the study site for its adherence to the clinical study protocol and GCP guidelines and applicable regulatory requirements.

11.2. Regulatory Agency Auditing

The PI must be aware that representatives from regulatory authorities or the IRB may wish to inspect the eCRFs and associated study records. The PI will notify the Sponsor within 24 hours following contact by a regulatory agency. The PI and study coordinator must make the relevant records available for inspection and will be available to respond to reasonable requests and audit queries made by authorized representatives of regulatory agencies. The PI will provide the Sponsor with copies of all correspondence that may affect the review of the current study or his qualification as an investigator in clinical studies conducted by the Sponsor. The Sponsor will provide any needed assistance in responding to regulatory audits or correspondence.

12. OBLIGATIONS AND ROLES OF THE SPONSOR, PI AND STUDY PERSONNEL

This study will be conducted according to GCP and in accordance with all federal regulations regarding the protection of human participants in research including US 21 CFR Part 50 and US 21 CFR Part 312. The PI agrees to perform the research in strict accordance with this protocol, the International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (E6), as well as in conformity with any federal, state, or local regulations regarding the conduct of clinical studies.

In addition, the PI must follow local and institutional requirements including, but not limited to, investigational product, clinical research, informed consent and IRB regulations. The Sponsor will provide notification to the PI of protocol and amendment approvals by regulatory authorities when applicable. Any modifications to the research protocol, the ICF, and/or the questionnaires or change in PI must be submitted to UMB IRB for review and approval prior to implementation. The

PI may deviate from the protocol without prior approval only when the deviation is necessary to eliminate an apparent immediate hazard to the participant.

The PI will notify UMB IRB of SAEs and protocol deviations according to UMB IRB requirements.

Any deviation to the protocol that may have an effect on the safety or rights of the participant, or the integrity of the study, must be reported to the Sponsor by the PI as soon as the deviation is identified. In that event, the PI will notify the Emmes/Sponsor immediately by phone, notify UMB IRB, enter the deviation into the appropriate eCRF, and confirm notification to the Sponsor in writing within ten working days after the change is implemented. All deviations will be noted in the continuing review report to and UMB IRB, the annual report to the Sponsor, and in the final study report for and UMB IRB.

Except where the PI's signature is specifically required, it is understood that the term "investigator" as used in this protocol and on the eCRFs refers to the PI or appropriate study personnel that the PI designates to perform a certain duty. The PI is ultimately responsible for the conduct of all aspects of the study. Sub-investigators or other appropriate study personnel are eligible to sign for the PI on designated eCRFs.

The Emmes medical monitor will be responsible for reviewing all serious and unexpected AEs and providing an unbiased written report of the event.

13. ETHICAL CONSIDERATIONS AND INFORMED CONSENT

13.1. Informed Consent Process

Before any study-related activities and in agreement with applicable regulatory requirements, the PI must ensure that the participant is fully informed about the aims, procedures, potential risks, and potential benefits of the study. The participant will be given the written, IRB approved ICF, allowed ample time to read the consent form, encouraged to ask questions about the study, have the questions answered and then be given time to decide if s/he would like to participate in the study. It will be emphasized that participation is voluntary, and that the participant has the right to withdraw from the study at any time without prejudice.

The PI or designee must obtain the participant’s voluntary, personally signed and dated ICF before any study-related procedures. The original, signed ICF must be kept in the site study file.

13.2. Risk/Benefit

No benefits can be guaranteed to participants for their participation in this research study.

Risks from Vaccine

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine. The mainstay in the treatment of severe anaphylaxis is the prompt use of adrenaline, which can be lifesaving.

Post vaccination, the participant should remain under the observation of not less than 60 minutes for occurrences of immediate or early allergic reactions. Corticosteroids and antihistaminics should also be available in addition to supportive measures such as oxygen inhalation and intravenous fluids (IV fluids).

This being a Phase 1 trial there is no safety data available with the use of MCV-5 vaccine. This trial aims to generate the same.

In clinical trials of Menactra®, most commonly reported injection site reactions following vaccination among adults were injection site pain (53.9%), induration (17.1%), redness (14.4%) and swelling (12.6%). In the same population, commonly reported systemic reactions were headache (41.4%), fatigue (34.7%), malaise (23.6%), arthralgia (19.8%), diarrhea (16.0%) and anorexia (11.8%), chills (9.7%) and vomiting (2.3%). All these are the frequencies reported within seven days of single vaccine dose. SAEs occurred in these individuals at a rate of 1.0% following Menactra® vaccine.[23]

It is expected that the solicited reactions with adjuvanted and non-adjuvanted MCV-5 would be consistent with those reported in clinical trials of Menactra®.

Risks from blood draw

Drawing peripheral blood can cause discomfort; it might cause minor bleeding and/or bruising where the needle enters the skin, and very rarely might cause infection. This risk will be mitigated by ensuring that only study staff members who are adequately trained in safe drawing of blood conduct this portion of the study. It is not anticipated that the risks in any one of the vaccine groups would be higher than others.

Risks from participating in a clinical trial

In addition to the risks described above, all clinical trial participants are likely to experience increased inconvenience due to the visits as they may be of longer duration than standard treatment, which might cause more anxiety. They also incur additional risks to their privacy from participating in a clinical trial. This risk will be minimized by ensuring that participant confidentiality is maintained by enforcing appropriate data collection, storage, and analysis techniques and employing the use of unique identifiers with carefully stored linking files. There may be additional risks to study trial participation that we do not know about.

13.3. Protocol Review Process

Scientific review of this protocol will be conducted by PATH, the sponsor of the study. The protocol will be submitted under a new IND. Protocol ethical review and oversight will be performed by UMB IRB. Continuing review will be undertaken in accordance with existing regulations. The Sponsor will be responsible for trial registration at ClinicalTrials.gov.

Copies of the approved continuing review and final study reports, along with the respective local IRB approval notifications, will be submitted to the Sponsor as soon as these documents become available.

13.4. Participant Confidentiality

The PI must ensure that participant confidentiality is maintained. Personal identifiers will not be included in any study reports. All study records will be kept confidential to the extent provided by national and local laws.

All study procedures will be conducted per GCP guidelines, and every effort will be made to protect participant privacy and confidentiality to the extent possible.

All study-related information will be stored securely at the study site or at a designated, secure off-site location. When not in use and under immediate control of study staff, all participant information will be stored in locked areas with access limited to study staff. Data collection, process, and administrative forms, laboratory specimens, and other reports will be identified exclusively by a coded number to maintain participant confidentiality. All local databases will be secured with password-protected access systems. Participants' study information will not be released without their written permission, except as necessary for monitoring or compliance with legal or regulatory requirements.

Medical records containing identifying information may be made available for review when the study is monitored by the sponsor or an authorized regulatory agency. Direct access may include examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

13.5. Reimbursement

Pending IRB approval, participants will be compensated for their time and effort in this study, and be reimbursed for travel to study visits. The study ICF will state the plan for reimbursement. Study participants will not be charged for study vaccinations, research clinic visits, research-related examinations, or research-related laboratory tests.

13.6. Storage of Specimens

Stored study research samples (including samples retained for elective analysis) will be labeled by a code that only the study site can link to the participant. All stored research samples will be logged into a secure database and any use documented. Samples may be stored at several different repositories and laboratories to complete the analyses required to meet study primary, secondary and exploratory analyses. As a part of the informed consent process, participants will be informed of and asked to agree to long-term storage of specimens for use in future, related research.

14. APPENDICES

14.1. APPENDIX I: Schedule of Events

Study visit	Visit 1 / screening	Visit 2	Visit 3	Visit 4	Visit 5	Final Study Contact
Study Day	$D_{-28\ to-1}$	D_1	D_{8+3}	D_{29+14}	D_{85+14}	$D_{180\pm21}$
Informed Consent	√	-	-	-	-	-
Demographics	√					
Medical history	√	√[A]	√[A]	√[A]	√[A]	√ (For SAEs)
Prior and concomitant medications	√	√	√	√	√ (For SAEs)	√ (For SAEs)
Physical examination	√	√[B]	√[B]	√[B]	√[B]	-
Pregnancy test [F] (female only)	√	√		√	√	-
Vital signs	√	√	√	√	√	-
Safety laboratory evaluation[C]	10 mL	-	8 mL	-	-	-
Screening for HIV, hepatitis B and C[D]	8 ml					-
Eligibility criteria	√	√	-	-	-	-
Randomization of eligible participants	-	√	-	-	-	-
Vaccination	-	√	-	-	-	-
Visual inspection of injection site		√	√			-
Memory card review and collection	-	√	√		-	-
Observe for 60 minutes: Assess and record post vaccine reactions	-	√	-	-	-	-
Immunogenicity Blood collection	-	20 mL[E]		30 mL	-	-
Cumulative blood volume	18 mL	20 mL	8 mL	30 mL		
Adverse event reporting		Solicited local and systemic reactions				
		Adverse Events				
		Serious Adverse Events				

A. Updated medical history only
B. Targeted physical examination, as indicated
C. Complete blood count (CBC): WBC, Hemoglobin, Platelets, Chemistry panel: ALT, Creatinine, Albumin, Total bilirubin
D. HBsAg, anti-HCV (if positive, by PCR), HIV EIA
E. Before vaccination
F. Only in case of female participants with child bearing potential. At the time of screening a serum pregnancy test will be performed whereas on the day of vaccination, urine or serum pregnancy test will be performed

14.2. APPENDIX II: Toxicity Grading Scale

[Replace the following blank pages with the Appendix PDF.]

14.3. APPENDIX III: References

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