First-in-Human Safety and Immunogenicity Evaluation of an Intramuscular *Campylobacter jejuni* Conjugate Vaccine (CJCV2) with and without Army Liposome Formulation containing QS-21 (ALFQ)

DMID Protocol Number: 19-0003

DMID Funding Mechanism: HHSN27201300016I

IND Sponsor: DMID

Principal Investigator: Robert W. Frenck, Jr, M.D.

DMID Clinical Project Manager: Peter Wolff, MHA

Draft or Version Number: 6.0

8 May 2023

STATEMENT OF ASSURANCE

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

STATEMENT OF COMPLIANCE

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

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

SIGNATURE PAGE

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

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

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

Site Investigator Signature:

Signed: _____ Date: _____

Name: Robert W. Frenck, Jr, M.D.

Title: Principal Investigator

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

3D-PHAD®	Monophosphoryl 3-deacyl lipid A (synthetic)
AE	Adverse Event/Adverse Experience
AH	Aluminum hydroxide
ALF	Army Liposome Formulation
ALFQ	Army Liposome Formulation containing QS-21
ALS	Antibodies in Lymphocyte Supernatant
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
BMI	Body Mass Index
BP	Blood Pressure
bpm	Beats Per Minute
CCHMC	Cincinnati Children's Hospital Medical Center
CCV	Capsule-Conjugate Vaccine
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practices
CHIM	Controlled Human Infection Model
CI	Confidence Interval
CJCV2	*Campylobacter jejuni* Conjugate Vaccine 2
CMS	Clinical Materials Services
CPS	Capsular Polysaccharide

CRF	Case Report Form
CRM_{197}	Cross-Reactive Material 197
CROMS	Clinical Research Operations and Management Support
CSR	Clinical Study Report
DDE	Direct Data Entry
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHS
eCRF	Electronic Case Report Form
ELISA	Enzyme-Linked Immunosorbent Assay
FDA	Food and Drug Administration
FoodNet	Foodborne Diseases Active Surveillance Network
FWA	Federal Wide Assurance
GBS	Guillain-Barré Syndrome
GCP	Good Clinical Practice
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Antibody
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
HLA-B27	Human Leukocyte Antigen B27
HR	Heart Rate
IB	Investigator's Brochure
IBD	Inflammatory Bowel Disease

IBS	Irritable Bowel Syndrome
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDES	Internet Data Entry System
IEC	Independent or Institutional Ethics Committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IM	Intramuscular
IND	Investigational New Drug Application
IRB	Institutional Review Board
LOS	Lipooligosaccharide
MAAE	Medically Attended Adverse Event
MedDRA®	Medical Dictionary for Regulatory Activities
MeOPN	*O*-methyl phosphoramidate
mITT	Modified Intent-to-Treat
MOP	Manual of Procedures
MPLA	Monophosphoryl Lipid A
N	Number (typically refers to subjects)
NIAID	National Institute of Allergy and Infectious Diseases, NIH, DHHS
NIH	National Institutes of Health
NMRC	Naval Medical Research Center

NOCMC	New-Onset Chronic Medical Condition
OER	Office of Extramural Research
OHRP	Office of Human Research Protections
OTC	Over the Counter
PBF	Pilot Bioproduction Facility
PBMC	Peripheral Blood Mononuclear Cell
PI	Principal Investigator
PIMMC	Potentially Immune-Mediated Medical Condition
PLT	Platelets
PP	Per protocol
QA	Quality Assurance
QC	Quality Control
RCD	Reverse Cumulative Distribution
SAE	Serious Adverse Event/Serious Adverse Experience
SAP	Statistical Analysis Plan
SDCC	Statistical and Data Coordinating Center
SMC	Safety Monitoring Committee
SOC	System Organ Class
SOP	Standard Operating Procedure
SRC	Safety Review Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
SWI	Sterile Water for Injection
T. bili	Total Bilirubin

UIP	University of Iowa Pharmaceuticals
US	United States
USP	United States Pharmacopeia
VTEU	Vaccine and Treatment Evaluation Unit
WBC	White Blood Cell Count
WRAIR	Walter Reed Army Institute for Research

PROTOCOL SUMMARY

Title:	First-in-Human Safety and Immunogenicity Evaluation of an Intramuscular *Campylobacter jejuni* Conjugate Vaccine (CJCV2) with and without Army Liposome Formulation containing QS-21 (ALFQ)
Design of the Study:	This is a randomized, double-blind, dose-escalating, outpatient trial in a total of approximately 60 subjects, assigned to 3 cohorts (20 subjects per cohort) (**Table 1**). Each subject will receive one of three intramuscular (IM) vaccinations with CJCV2 (1 µg, 3 µg or 10 µg of capsular polysaccharide (CPS) conjugated to cross-reactive material 197 (CRM_{197})) spaced 28 days between injections, without or with a fixed dose of the adjuvant ALFQ (200 µg 3D-PHAD® and 100 µg QS-21 in Sorensen's Phosphate Buffered Saline). As this is a first-in human study, there will be six sentinel subjects in each of the 3 cohorts. No more than two sentinels will be dosed per day with a minimum of two hours between dosing. All sentinels will be observed for at least 7 days after which a safety review will be conducted. If no safety signal is detected, the remaining 14 participants in the cohort will be dosed.
Study Phase:	Phase 1
Study Population:	Healthy male and non-pregnant, non-lactating female subjects, 18-50 years of age, inclusive.
Number of Sites:	1

Description of Study Product or Intervention:	The investigational products are the vaccine CJCV2 and the adjuvant ALFQ. CJCV2 is a purified HS23/36 CPS of *Campylobacter jejuni* conjugated to CRM_{197}. ALFQ consists of two active components, a synthetic monophosphoryl lipid A, 3D-PHAD® and QS-21, a purified saponin extracted from the bark of the *Quillaja saponaria* tree. Three doses (1 ug, 3 ug and 10 ug) of CJCV2 will be evaluated. The first six participants at each dose will be sentinels and randomized in a 1:1 blinded fashion to receive CJCV2 with or without ALFQ.
Study Objectives:	**Primary** • Evaluate the safety of three different doses of IM injection of CJCV2 with and without ALFQ **Secondary** • Evaluate *C. jejuni* capsule-specific serum Immunoglobulin G (IgG) responses following vaccination **Exploratory** • Evaluate CRM_{197}-specific serum-IgG responses • Evaluate *C. jejuni* capsule-specific IgG in Antibody Lymphocyte Supernatant (ALS) • Evaluate *C. jejuni* capsule- and CRM_{197}-specific serum Immunoglobulin M (IgM) responses **Secondary Research** • Peripheral blood mononuclear cells (PBMCs), serum, and stool samples will be collected and stored for future use

	to further characterize immune responses following vaccination.
Duration of Individual Subject Participation:	Approximately 15 months
Estimated Time to Last Subject/Last Study Day:	Approximately 24 months

1 KEY ROLES

This study is sponsored by DMID. Decisions related to this study will be made by the protocol team, which includes representatives from the participating clinical research site (Principal Investigator) and DMID (sponsor). Key Roles are noted in the protocol-specific manual of procedures (MOP).

1.1 Background

Campylobacter species are among the most common causes of diarrheal disease worldwide with *C. jejuni* being the primary species associated with human disease [1]. Campylobacteriosis ranges from hyperendemic levels (prevalence up to 84.9% in children <1 year of age) in developing regions [2], to sporadic disease in young adults and infants, in developed countries [3], or traveler's diarrhea in persons from industrialized countries, including deployed troops, visiting hyperendemic regions [4-7]. *Campylobacter* is one of the most severe forms of travelers' diarrhea with a longer duration, increased numbers of unformed stools, and more frequent association with abdominal pain, nausea, vomiting and fever in comparison to the other common causes [3, 5, 7-9]. In addition to the acute effects, *Campylobacter* infection is associated with a number of important sequelae, including Guillain-Barré syndrome (GBS), reactive arthritis, irritable bowel syndrome and, to a lesser extent, inflammatory bowel disease [10-15].

- **Public health impact and current standard of care for treatment/prevention**

Campylobacter is the most common bacterial cause of foodborne illnesses in the US; in 2016 the Centers for Disease Control and Prevention (CDC) Foodborne Diseases Active Surveillance Network (FoodNet) reported 24,029 foodborne infections, 5,512 hospitalizations, and 98 deaths [3]. Globally, *Campylobacter* is 1 of the 4 key global causes of diarrheal diseases [9]. The high incidence of *Campylobacter* diarrhea, as well as its duration and possible complications, makes it highly important from a socio-economic perspective. In developing countries, *Campylobacter* infections in children under the age of 2 years are especially frequent, sometimes resulting in death. Until recently, campylobacteriosis has been viewed as a self-limited illness ameliorated by antibiotic treatment. However, the resistance of *Campylobacter* to many antibiotics, particularly fluoroquinolones, is rapidly rising as a single point mutation is sufficient for the development of resistance [16-18]. Thus, alternative measures to control the infection, including vaccination, are required.

1.2 Scientific Rationale

1.2.1 Purpose of Study

This is a first-in-human study to test the safety and immunogenicity of a vaccine comprised of a CPS of *C. jejuni* conjugated to CRM_{197} and whether ALFQ will enhance the immune response without significantly altering safety of CJCV2. The study hypothesis is that the CJCV2 vaccine alone and CJCV2 + ALFQ adjuvant will be safe and that the CJCV2 alone will be immunogenic, with immunogenicity enhanced through the use of the adjuvant ALFQ.

1.2.2 Study Population

As this is the first time the CJCV2 ± ALFQ will be tested in humans, the study population will be comprised of generally healthy males and non-pregnant, non-lactating females, aged 18-50 years inclusive at the time of first vaccination, regardless of religion, sex, or ethnic background, who meet all the inclusion and none of the exclusion criteria. Subjects will be recruited from the general population of the participating Vaccine and Treatment Evaluation Unit (VTEU) site. As this is a Phase 1 study, minors and pregnant or breastfeeding women will be excluded from study participation. A successful outcome of the current trial may lead to future evaluation of the study product which then may incorporate a broader participant population including children.

1.3 Potential Risks and Benefits

1.3.1 Potential Risks

CJCV2 is a vaccine comprised of *C. jejuni* capsule conjugated to CRM_{197} that will be administered IM using standard techniques. The IM route of vaccination, in general, has been shown to be a safe and effective route of administration. Based on the safety results of the CJCV1 clinical trial as well as other studies evaluating IM administration of conjugated vaccines, it is anticipated that subjects may experience pain, redness, and/or swelling at the injection site.

Additionally, general symptoms of fever, fatigue, headache, muscle aches, joint aches, malaise, and nausea/vomiting may also occur. Any vaccine may be associated with a wide range of systemic events, and the frequency and type of systemic reactions will be addressed and analyzed with respect to study products.

Theoretical Risks

Post-infectious sequelae following *Campylobacter* enteritis must be considered as theoretical risks with a *Campylobacter* capsule-conjugate vaccine (CCV). *Campylobacter* infections have been associated with the development of reactive arthritis [19-24] and GBS [25-27]. Possibly as many as 1% of *C. jejuni* enteritis cases may be followed approximately 10 days post-infection with reactive arthritis characterized as an asymmetric oligoarticular arthritis commonly involving the knees, ankles, or wrists. A proportion of the patients reported to have *Campylobacter*-associated post-infectious reactive arthritis are human leukocyte antigen B27 (HLA-B27) positive. Although the majority (approximately 80%) of patients with reactive arthritis associated with an enteric infection become asymptomatic within one year, as many as 20% may relapse. The pathogenesis for a post-infectious reactive arthritis is less understood. Although it is unlikely to be related to the purified *Campylobacter* capsule, there is enough uncertainty to include specific entry criteria related to this theoretical risk by excluding a volunteer if positive for HLA-B27 or if the volunteer or a first-degree relative (parent or sibling) has a history of inflammatory arthritis.

The pathogenesis of GBS is not fully understood; however, it is thought to be an autoimmune response against peripheral nerves due to a molecular mimicry between *Campylobacter* lipooligosaccharide (LOS) cores containing sialic acid structures that resemble human nerve tissue gangliosides [28-30]. Certain heat-stable serotypes (correlating with the Penner typing system but still with strain-to-strain variation) contain a carbohydrate portion of the LOS that mimics certain mammalian tissue gangliosides (particularly GM_1, GD_{1a} and GQ_{1b}) that are components of nerve tissue (myelin sheath and/or axon). This mimicry may lead to the induction of anti-ganglioside antibodies that in some yet undetermined way led to immune-mediated damage to nerve fibers. To minimize risk of GBS, the polysaccharide used to synthesize the CJCV2 vaccine was extracted from a mutant of 81-176 (strain PG3208.1) that lacks ganglioside mimicry in its LOS core. Importantly, there has been no association between the *Campylobacter* capsule and GBS risk. Therefore, subjects receiving the CJCV2 vaccine are not considered to be at risk of developing GBS.

1.3.1.1 ALFQ

This family of adjuvants formulation containing saturated phospholipids, cholesterol, and monophosphoryl lipid A (MPLA) is known as Army Liposome Formulation or ALF. ALFQ is a phospholipid: cholesterol liposome containing a combination of synthetic monophosphoryl lipid A (MPLA; 3D-PHAD® (Avanti Polar Lipids, Alabaster, AL)) and QS-21 (Desert King, San

Diego, CA), a purified saponin extracted from the bark of the Quillaja saponaria tree. Forms of MPLA have been used in many previous clinical trials. MPLA is the active component of lipopolysaccharide (i.e., endotoxin). Encapsulation of MPLA in liposomes detoxifies MPLA, since the toxic fatty acids are buried in the lipid bilayer. Walter Reed Army Institute of Research (WRAIR) liposomes containing MPLA have been safely used in fourteen Phase 1 and two Phase 2 clinical trials. QS-21 (Q component of ALFQ) as an adjuvant, has been studied in many clinical trials for human immunodeficiency virus (HIV), malaria, hepatitis B, and cancer. In the past, subjects immunized with QS-21-adjuvanted vaccines have reported mild to moderate local and systemic responses. In addition, QS-21 is a component of AS01B, which has been used safely as the adjuvant in the Shingrix®vaccine. Additionally, ALFQ has been administered to subjects participating in a trial to evaluate a vaccine against malaria (NCT04296279, NCT04268420), and preliminary safety data are summarized in **section 3.1.2**. The current trial will provide additional experience with ALFQ as a vaccine adjuvant.

1.3.1.2 IM Vaccination

Expected local adverse events (AEs) of IM vaccine administration include pain/tenderness, redness, and induration/swelling/nodules at the site of vaccination.

1.3.1.3 Blood Collection

Drawing blood may cause transient discomfort and may cause people to feel faint. Bruising at the blood draw site may occur but can be prevented or lessened by applying pressure for several minutes. Infection at the site of blood collection is a rare but possible event. Rarely, infection or a blood clot may develop. Risks of blood collection will be minimized by using sterile technique and having experienced personnel perform the blood collection.

1.3.1.4 Other Risks

The inclusion and exclusion criteria have been constructed to selecta population of healthy adults which should minimize the risks to study participants. However, unrecognized risks may still be associated with administration of the vaccine.

As with any Investigational New Drug (IND) product administration and no matter what precautions are taken, there is always the risk of a serious, or even life-threatening, allergic reaction. Although anaphylactic reactions are not anticipated, as with any vaccination, the rare possibility exists. For this reason, all subjects will be observed at the study site for a minimum of 30 minutes following vaccine dosing. Appropriate emergency equipment (e.g., automated external defibrillator, air-shields manual breathing unit bag) and medication [e.g., antihistamines

and adrenaline (epinephrine)] for initial treatment of an allergic reaction will be available at the site whenever immunizations are given. This equipment is available to handle emergencies such as anaphylaxis, angioedema, bronchospasm, and laryngospasm.

Because the risks of the vaccine to a pregnant or nursing woman or fetus are unknown, pregnancy is an exclusion and women of childbearing potential will be counseled against becoming pregnant during their participation in the study.

1.3.2 Known Potential Benefits

There are no direct medical benefits to the subject because of study participation. However, participation could benefit society by developing data about the safety, tolerability, and immunogenicity of this candidate vaccine against *C. jejuni* infection. These data will be instrumental in further development of a *Campylobacter* vaccine for licensure. Development of an efficacious vaccine against *C. jejuni* would significantly improve the health of children living in *Campylobacter*-endemic areas, as well as adults traveling to such areas.

2 STUDY DESIGN, OBJECTIVES AND ENDPOINTS OR OUTCOME MEASURES

2.1 Study Design Description

This is a randomized, double-blind, dose-escalating, outpatient, first-in-human study to test the safety and immunogenicity of a vaccine comprised of a CPS of *C. jejuni* conjugated to CRM_{197} and whether ALFQ will enhance the immune response without significantly altering safety.

Sixty subjects, divided into 3 cohorts (20 subjects per cohort), will receive three IM vaccinations spaced 28 days apart. Each subject will be administered CJCV2 with or without a fixed dose of the adjuvant ALFQ (1:1 allocation, CJCV2:CJCV2+ALFQ). A range of vaccine doses (1 µg, 3 µg and 10 µg) will be evaluated in the study. These doses were picked as 1 µg is thought to be the lowest dose that will stimulate an immune response, 3 µg is likely to stimulate an effective immune response, and 10 µg is the highest dose that would be practical to use in a multivalent vaccine (the long-term plan for a vaccine against *Campylobacter*). The three-dose regimen and use of ALFQ was based on previous evaluation of a 1st generation *Campylobacter* vaccine named CJCV1 which demonstrated that 2 doses of vaccine using aluminum hydroxide (AH) as an adjuvant was safe, but immunogenicity was poor. As this is the first time the CJCV2 vaccine will be tested in humans, the study population will be comprised of generally healthy young adults (male and non-pregnant or -lactating female) 18-50 years of age, inclusive (See **Table 1** below for dosing scheme).

Table 1: Table of Study Design

Cohort [a]	Group [b]	N	CJCV2 (µg)	ALFQ
1	Sentinel 1-A [c]	3	1	0
	Sentinel 1-B [c]	3	1	200 µg 3D-PHAD®, 100 µg QS-21
	1-A	7	1	0
	1-B	7	1	200 µg 3D-PHAD®, 100 µg QS-21
2	Sentinel 2-A [c]	3	3	0
	Sentinel 2-B [c]	3	3	200 µg 3D-PHAD®, 100 µg QS-21
	2-A	7	3	0
	2-B	7	3	200 µg 3D-PHAD®, 100 µg QS-21
3	Sentinel 3-A [c]	3	10	0
	Sentinel 3-B [c]	3	10	200 µg 3D-PHAD®, 100 µg QS-21
	3-A	7	10	0
	3-B	7	10	200 µg 3D-PHAD®, 100 µg QS-21

Note: Subjects will receive vaccinations on study days 1, 29, and 57.

a. SRC Review (PI, Medical Officer, Medical Monitor) through the final vaccine reactogenicity period for each cohort prior to dose escalation.
b. Sentinels in each cohort will be randomized 1:1 in a blinded fashion to receive CJCV2 with or without ALFQ. Sentinels will be dosed at least 2 hours apart with no more than 2 sentinels per day.
c. SRC Review (PI, Medical Officer, Medical Monitor) 7-9 days after the first dose. SRC review after second and third doses in Sentinel groups will be completed only if a stopping rule is met.

Vaccine safety will be assessed by evaluating post-vaccination local and systemic reactions through targeted physical exams, symptom surveys and other AE monitoring. All subjects will be observed in the clinic for at least 30 minutes after receipt of the investigational product. Subject e-memory aid data entered via web-based e-memory aid will be reviewed by the study team for AEs during the collection period. After review and reconciliation, data from the study e-memory aid will be transferred by study staff into the electronic Case Report Form (eCRF). Virtual visits will be performed at 48 hours and outpatient clinic visits will be performed 7 days

after study vaccine administration for observation and reporting of any local and/or systemic AE's. Additionally, if a subject were to experience an unanticipated AE, an unscheduled clinic visit may be conducted.

Three doses (1 ug, 3 ug and 10 ug) of CJCV2 will be evaluated. The first six participants at each dose will be sentinels and randomized in a 1:1 blinded fashion to receive CJCV2 with or without ALFQ. Sentinels will be dosed at least two hours apart with no more than two sentinels per day vaccinated. Sentinels will be observed for at least 7 days after which a safety review will be conducted. If no safety signal is detected, the remaining 14 participants in the cohort will be dosed using the same randomization scheme for the sentinels. This sentinel design will be followed for Cohorts 2 and 3.

Assuming no safety concerns arise after review of the first cohort, the dose of CJCV2 will be raised to 3 μg for the second cohort. Similar rationale and plan will be used to escalate to Cohort 3. The investigational products will be co-formulated just prior to IM injection.

Between the time of vaccination of the first six sentinels to 7 days after enrollment of the last sentinels, no new subjects will be vaccinated, but screening may continue. The Safety Review Committee (SRC) will review safety data following the first dose of the six sentinel subjects in each cohort, and again after each cohort has completed vaccination, to decide if the study may proceed to the next dosage level. SRC members include the Principal Investigator (PI), the DMID Medical Monitor, and the DMID Medical Officer, with input provided from Emmes.

2.2 Study Objectives

- **Primary**
  - Evaluate the safety of the three different doses of IM injection of CJCV2 with and without ALFQ

- **Secondary**
  - Evaluate *C. jejuni* capsule-specific serum IgG responses following vaccination

- **Exploratory**
  - Evaluate CRM_{197}-specific serum IgG responses

  - Evaluate *C. jejuni* capsule-specific IgG in ALS

- Evaluate *C. jejuni* capsule-and CRM_{197}-specific serum IgM responses

- **Secondary Research**
  - PBMCs, serum, and stool samples will be collected and stored for secondary research to further characterize immune responses following vaccination.

2.3 Study Endpoints or Outcome Measures

- **Primary**
  - Occurrence of solicited local and systemic AEs through 7 days after each study vaccination
  - Occurrence of vaccine-related unsolicited AEs through 28 days post last vaccination
  - Occurrence of serious adverse events (SAEs) through approximately 12 months post last vaccination
  - Occurrence of medically attended adverse events (MAAEs), new-onset chronic medical conditions (NOCMCs), and potentially immune-mediated medical conditions (PIMMCs) from the time of the first study vaccination through approximately 12 months (or throughout the period of their study participation) following the last vaccination
- **Secondary**
  - Development of a ≥ 4-fold rise from baseline in *C. jejuni* capsule-specific IgG serum antibodies at Days 8, 29, 36, 57, 64, 85 and 113
  - Peak fold rise from baseline in *C. jejuni* capsule-specific IgG serum antibody titer across Days 8, 29, 36, 57, 64, 85 and 113
  - Maximum *C. jejuni* capsule-specific IgG serum antibody titer across Days 8, 29, 36, 57, 64, 85 and 113
- **Exploratory**

  CRM_{197} IgG

  - Development of a ≥ 4-fold rise from baseline in CRM_{197}-specific IgG serum antibodies at Days 8, 29, 36, 57, 64, 85 and 113
  - Peak fold rise from baseline in CRM_{197}-specific IgG serum antibody titer across Days 8, 29, 36, 57, 64, 85 and 113

- Maximum CRM_{197}-specific IgG serum antibody titer across Days 8, 29, 36, 57, 64, 85 and 113

ALS CPS IgG

- Development of a ≥ 4-fold rise from baseline in *C. jejuni* capsule-specific IgG antibodies in lymphocyte supernatant at Days 8, 36 and 64
- Peak fold rise from baseline in *C. jejuni* capsule-specific IgG antibodies in lymphocyte supernatant across Days 8, 36 and 64
- Maximum *C. jejuni* capsule-specific IgG antibodies in lymphocyte supernatant titer across Days 8, 36 and 64

Serum IgM

- Development of a ≥ 4-fold rise from baseline in *C. jejuni* capsule-specific serum IgM at Days 8, 29, 36, 57, 64, 85 and 113
- Development of a ≥ 4-fold rise from baseline in CRM_{197}-specific serum IgM at Days 8, 29, 36, 57, 64, 85 and113
- Peak fold rise from baseline in *C. jejuni* capsule-specific serum IgM titer across Days 8, 29, 36, 57, 64, 85 and 113
- Peak fold rise from baseline in CRM_{197}-specific serum IgM titer across Days 8, 29, 36, 57, 64, 85 and 113
- Maximum *C. jejuni* capsule-specific serum IgM titer across Days 8, 29, 36, 57, 64, 85 and 113
- Maximum CRM_{197}-specific serum IgM titer across Days 8, 29, 36, 57, 64, 85 and 113

- **Secondary Research**

  - Storage of
    - Serum
    - PBMC
    - Stool

3 STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

3.1 Study Product Description

3.1.1 CJCV2

The vaccine to be evaluated in the current project is a *C. jejuni* CCV named CJCV2 produced from an engineered mutant of 81-176 that is lacking an enzyme responsible for the production of a LOS that could potentially trigger GBS. In contrast to the strain used for CJCV1 (which was made from strain 3208), a natural variant of 3208 (named 3208.1) was selected that presents the two *O*-methyl phosphoramidate (MeOPN) transferases in the "on" status to ensure that there is an optimum amount of MeOPN on the capsule. The CPS is conjugated to CRM_{197}, a non-toxic mutant protein of diphtheria toxin at a CPS: CRM_{197} ratio of 2:1. The CJCV2 vaccine product was manufactured at Inventprise LLC (Redmond, Washington) with final fill and finish completed by The University of Iowa Pharmaceuticals (Iowa City, Iowa), both performed under current Good Manufacturing Practices (cGMP) conditions.

- **Role of this study in clinical development**

This will be a Phase 1, first-in-human study of CJCV2 (1, 3, or 10 µg), with or without a fixed dose of ALFQ (200 µg 3D-PHAD®and 100 µg QS-21) to evaluate the safety and immunogenicity of the vaccine. A successful study will provide data for an increased number of subjects to receive an optimal CJCV2 dose (with or without adjuvant), and to potentially evaluate vaccine efficacy in a controlled human infection model (CHIM) with *C. jejuni* strain CG8421.

- **Prior studies of the study product**

Under US Army sponsorship, the Naval Medical Research Center (NMRC) recently completed a Phase 1, first-in-human trial with the prototype *C. jejuni* CPS vaccine conjugated to CRM_{197}, called CJCV1 (ClinicalTrials.gov Identifier: NCT02067676). The vaccine was manufactured using NIAID funding (NIH U01 AI082105) and delivered intramuscularly with AH. Forty-eight subjects (eight per group) received two doses of 2, 5, or 10 µg of the CJCV1 intramuscularly with or without 125 µg of AH on Days 0 and 28. There were no vaccine-related SAEs or unanticipated events. The vaccine was well-tolerated, with all vaccine-related AEs being mild to moderate vaccine site pain or tenderness. Irrespective of the CJCV1 dose delivered, only 6 of 48 subjects (12.5%) seroconverted against the CPS.

Several factors may have contributed to the sub-optimal immunogenicity, including: (1) insufficient dosing, (2) unconjugated CPS content, (3) low level MeOPN, (the apparent immunodominant epitope, on the capsule), and (4) AH being a suboptimal adjuvant. The possibility of insufficient dosing was addressed by adding a third dose on Day 57 (planned vaccination scheduled: Days 1, 29, 57). The levels of MeOPN have been addressed by manufacturing a new lot of the vaccine, yielding increased levels of MeOPN on the polysaccharide. Concerns with suboptimal adjuvant have resulted in additional preclinical testing of the vaccine combined with other adjuvant options, including ALF or ALFQ. Co-administration of the CCV (CJCV1) with ALF or the combination adjuvant ALFQ to mice resulted in a significantly higher immune response when compared to animals receiving the vaccine with AH. In non-human primates, a research-grade formulation of the *C. jejuni* CCV delivered with ALFQ showed a superior immune response. Additionally, the highest vaccine efficacy occurred in the animals vaccinated with the CCV and ALFQ admixture (**Table 2**).

Table 2: CCV vaccine efficacy in the *Aotus nancymaae* model with adjuvant

Group	No. of animals	Diarrhea attack rate, n (%)	Protective efficacy against diarrhea (%)	p- value*
CCV+AH	10	5 (50%)	29%	0.43
CCV+ALF	17*	4 (24%)	66%	0.008
CCV+ALFQ	10	1 (10%)	86%	0.005
PBS	20**	14 (70%)	-	

Three doses of 3.5 µg CCV given at 4-week intervals with the named adjuvants. Animals were orogastrically challenged 4 weeks following 3rd immunization with *C. jejuni* CG8421. *1 animal was excluded due to pregnancy **2 animals were excluded due to pre-existing health conditions

3.1.2 ALFQ

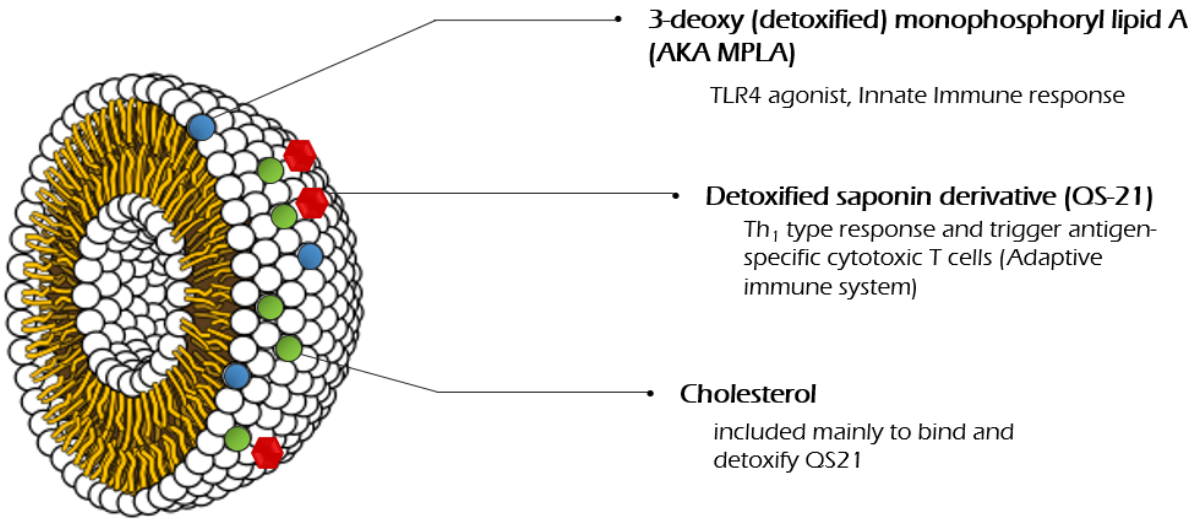


Figure 1. Description of the ALFQ adjuvant [31]

The vaccine will be co-administered with a combination adjuvant ALFQ. ALFQ is composed of ALF55, QS-21, and Sorensen's Phosphate Buffer. ALF55 is a cGMP-manufactured Army Liposome Formulation containing the phospholipids dimyristoyl phosphatidyl choline and dimyristoyl phosphatidyl glycerol, 3D-PHAD® and 55% cholesterol. Cholesterol serves as a structural lipid and binds to QS-21. QS-21 is a purified saponin extracted from the bark of the *Quillaja saponaria* tree. ALFQ was manufactured at the WRAIR Pilot Bioproduction Facility (Silver Spring, Maryland). A diagram of ALFQ is shown above in **Figure 1**.

ALFQ has been used in numerous non-human primates, mouse, and rabbit studies and was well tolerated. A recent publication evaluated a malaria vaccine administered with ALFQ adjuvant [32]. Three groups of six Rhesus monkeys received half or a full human dose of the malaria vaccine + ALFQ on a 0-1-2-month schedule. Animals had mild local site reactions with no changes in red blood cell, liver, or kidney lab values. Immunization induced a transient systemic inflammatory response, including elevated white blood cell counts (WBCs) and mild fever receding to normal range by Day 7 post vaccination. A four-dose GLP toxicity study in rabbits confirmed no local site reactions and transient systemic inflammation associated with ALFQ adjuvant administration. The good safety and immunogenicity profile of ALFQ in the animal studies resulted in the decision to move the product to a vaccination study/CHIM of malaria

which is active and ongoing (NCT04296279, NCT04268420). Volunteers in these studies received either low dose of one of two protein antigen vaccines with low dose of ALFQ adjuvant, or high dose of one of two protein antigen vaccines with high dose of ALFQ. ALFQ local reactogenicity in these studies appeared to be comprised primarily of local tenderness that is omnipresent, mild, and short-lived across both products and doses. Systemic reactogenicity primarily consisted of a flulike response that was also 24-36 hours in length that increased in intensity in the following order of dose and product: FMP013 low-dose (mostly absent or mild), FMP014 low-dose(mostly absent or mild), FMP013 high-dose (mild after first dose and mix of mild and moderate severities after 2nd and 3rd dose) , FMP014 high dose (mild to moderate severities after the first dose with mostly moderate severities after each dose with one subject having 24 hours of severe fever chills, myalgias, and moderate temperature of 101.5ºF after the third dose). There were no SAEs associated with ALFQ reported in these studies.

This proposed study will be the first time that the CJCV2 vaccine (either alone or in combination with ALFQ) will be administered to humans.

3.1.3 Packaging

CJCV2 vaccine – CJCV2 is lyophilized in single 2 mL glass vials. Each CJCV2 vial contains 60 µg of CPS and 40 µg CRM_{197} per vial of active components and excipients consisting of 8 mg Sodium Chloride; 0.7 mg Potassium Chloride; 0.8 mg Sodium Phosphate; 0.144 mg Potassium Phosphate, and 5.0 mg Sucrose. CPS is conjugated to CRM_{197} at a ratio of 2:1, CPS:CRM_{197}.

ALFQ adjuvant - Each single glass vial of ALFQ contains 0.6 mL and its active components are at a concentration of 400 µg/mL 3D-PHAD® and 200 µg/mL QS-21 in Sorensen's Phosphate Buffered Saline.

3.1.4 Formulation

The sterile lyophilized CJCV2 product is to be reconstituted in 1 mL of sterile water for injection (SWI). The resuspended CJCV2 product will be diluted with sterile 0.9% Sodium Chloride for Injection, United States Pharmacopeia (USP) to a bulk 2x CJCV2 working solution (Cohort A: 2 µg/mL, Cohort B: 6 µg/mL or Cohort C: 20 µg/mL).

For subject-specific formulation, a total of 0.6 mL of the bulk 2x CJCV2 working solution will be transferred and mixed with a vial containing 0.6 mL of the adjuvant ALFQ or 0.6 mL of sterile 0.9% Sodium Chloride for Injection, USP to prepare 1.2 mL of a final 1x CJCV2 formulation (Cohort 1: 1 µg/mL, Cohort 2: 3 µg/mL or Cohort 3: 10 µg/mL). One milliliter will be drawn into a syringe to be injected intramuscularly to achieve the final quantity of deliverable

active CJCV2 component as described above and the full dose of ALFQ (200 µg 3D-PHAD®, 100 µg QS-21) in subjects receiving the adjuvant plus CJCV2. Further details of formulation and administration are to be included in the MOP.

3.1.5 Labeling

Renderings of the CJCV2 (**Figure 2**) and ALFQ (**Figure 3**) labels are included.

Figure 2. CJCV2 Lot 010I0319 Label

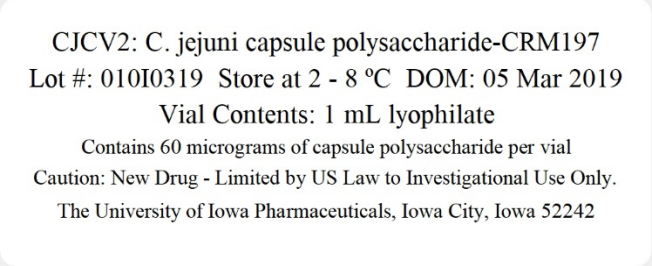
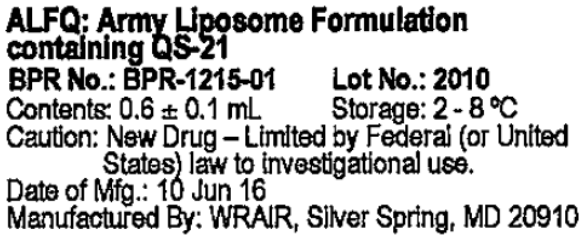


Figure 3. ALFQ Lot 2010 Label



3.1.6 Product Storage

CJCV2 vials are stored at refrigerated conditions (2°C-8°C).

ALFQ vials are stored at refrigerated conditions (2°C-8°C).

3.1.7 Product Stability

Separate stability studies are being conducted to assess CJCV2 and ALFQ stored at various temperatures.

To date, CJCV2 has shown stability through the 24-month time point with a plan to continue testing at 36- and 48-month timepoints. Detailed descriptions of the CJCV2 stability program are included in the Investigator's Brochure (IB).

The stability of ALFQ will be tested throughout the course of this study. The complete stability information can be found in the Drug Master File 18760.

3.2 Acquisition/Distribution

The CJCV2 product is stored at the University of Iowa Pharmaceuticals (UIP), [redacted]

The ALFQ product is stored at the WRAIR Pilot Bioproduction Facility (PBF), [redacted]

SWI will be provided by DMID Clinical Materials Services (CMS) Contract.

Sterile 0.9% Sodium Chloride for Injection, USP will be provided by DMID CMS Contract.

Upon DMID authorization, the CJCV2 and ALFQ will be transferred to the following address:

DMID Clinical Materials Services (CMS)
c/o Fisher BioServices
[redacted]
Germantown, MD 20876, U.S.A.
Tel: [redacted]
Fax: [redacted]
Email: [redacted]

All study products will be shipped to the Cincinnati Children's Hospital Medical Center (CCHMC) upon request and approval from DMID.

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

CJCV2 Bulk Preparation

CJCV2 will be administered intramuscularly in 3 doses separated by 28 days (Day 1, 29 and 57). Each lyophilized CJCV2 vial will be rehydrated with 1 mL SWI. A bulk 2x CJCV2 working solution will be prepared by diluting CJCV2 in sterile 0.9% Sodium Chloride for Injection, USP to obtain 2, 6, or 20 µg/mL suspension. This suspension will be used to prepare subject specific formulation as follows;

CJCV2 Alone;

A subject-specific formulation will be prepared by adding 0.6 mL of the bulk 2x CJCV2 working solution to 0.6 mL sterile 0.9% Sodium Chloride for Injection, USP to achieve a final 1x CJCV2 solution (1, 3 or 10 µg/mL) and 1 mL will be injected intramuscularly to deliver to respect cohorts.

CJCV2 + ALFQ

ALFQ is provided as suspension. A subject-specific formulation will be prepared by adding 0.6 mL of the bulk 2x CJCV2 working solution to 0.6 mL 2x ALFQ (product as provided; 400 µg/mL 3D-PHAD® and 200 µg/mL QS-21) to achieve a final 1x CJCV2 solution (1, 3 or 10 µg/mL) and 1x ALFQ solution (200 µg/mL 3D-PHAD®and 100 µg/mL QS-21 solution). Prior to administration, 1 mL of the CJCV2-ALFQ admixture will be drawn into a syringe for IM injection to respective cohorts.

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

CJCV2 will be shipped from UIP and ALFQ will be shipped from the WRAIR PBF to the DMID contract CMS for storage until sent to CCHMC. Once received, CJCV2 and ALFQ will be stored in and dispensed by the Investigational Pharmacy.

Used and unused study product vials will be retained until monitored and released for disposition, as applicable. This can occur on an ongoing basis for used study products.

Used study product vials may be destroyed in accordance with site-specific standard operating procedures (SOPs) following each monitoring visit where study product accountability is monitored, and resolution of any discrepancies.

Unused study product that has not been reconstituted may be destroyed or transferred for use in nonclinical research only according to the MOP once determined by DMID and communicated to the participating sites by the DMID Clinical Project Manager.

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

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

All used containers of study product may either; 1) be sequestered from the unused supplies and stored at 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature] in the Investigational Pharmacy until study completion or until study product accountability has occurred by the monitor and written notification stating retention is no longer required is received, or; 2) may be destroyed in accordance with site-specific SOPs with a second pharmacy staff member's observation and verification as documented in the pharmacy log and/or preparation worksheets.

4 SELECTION OF SUBJECTS AND STUDY ENROLLMENT AND WITHDRAWAL

Approximately 60 individuals, including males and non-pregnant females 18 to 50 years old, at the time of the first vaccination, who are in good health by history and screening values and meet the inclusion and exclusion criteria will be enrolled in the study. The eligibility criteria apply only to enrollment of subjects into the study. The target population should reflect the community at large at the site.

Subject inclusion and exclusion criteria must be assessed by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.

No exemptions are granted on subject inclusion or exclusion criteria in DMID-sponsored studies.

Questions about eligibility should be directed toward the DMID Medical Officer.

4.1 Eligibility Criteria

4.1.1 Subject Inclusion Criteria

1. Provide informed consent prior to initiation of any study procedures.
2. Able to understand and comply with planned study procedures and be available for all study visits/safety communications.
3. Non-pregnant/non-lactating subjects 18-50 years of age inclusive upon enrollment.
4. In general, good health* to be safely enrolled in this study as determined by medical history, medication use**, and physical exam.

   *Good health is defined by the absence of any exclusionary medical conditions. If the subject has another current, ongoing medical condition, the condition cannot meet any of the following criteria; 1) first diagnosed within 3 months of enrollment; 2) is worsening in terms of clinical outcome in last 6 months; or 3) involves need for medication that may pose a risk to subject's safety or impede assessment of AEs or immunogenicity if they participate in the study.
   ** Topical, nasal, and inhaled medications (except for inhaled corticosteroids as outlined in the Subject Exclusion #17). Herbals, vitamins, and supplements are permitted.
5. Oral temperature is less than 100.4°F.
6. Pulse is 50 to 100 beats per minute (bpm), inclusive.
7. Systolic blood pressure (BP) is 90 to 140 mmHg, inclusive.
8. Diastolic BP is 55 to 90 mmHg, inclusive.
9. Body Mass Index (BMI) less than 40.

10. Females of childbearing potential* may enroll if subject has practiced adequate contraception** > 30 days prior to enrollment and agrees to continue adequate contraception for the entire study.
    * Child-bearing potential is defined as not sterilized via tubal ligation, bilateral oophorectomy, salpingectomy, hysterectomy, or successful Essure® placement (permanent, non-surgical, non-hormonal sterilization) with documented radiological confirmation test at least 90 days after the procedure, and still menstruating or <1 year of the last menses if menopausal.
    ** Adequate contraception includes non-male sexual relationships, abstinence from sexual intercourse with a male partner, monogamous relationship with vasectomized partner who has been vasectomized for 180 days or more prior to the subject receiving the first study vaccination, barrier methods such as condoms or diaphragms with spermicide, effective intrauterine devices, NuvaRing®, and licensed hormonal methods such as implants, injectables, or oral contraceptives ("the pill").
11. Females of childbearing potential must have a negative urine pregnancy test within 24 hours prior to enrollment.
12. Agree not to participate in another interventional clinical trial during the study period that may affect the analysis or endpoint assessment.
13. Negative urine drug screen for opiates.

4.1.2 Subject Exclusion Criteria

1. Have any disease or medical condition that, in the opinion of the site PI or appropriate sub-investigator, is a contraindication to study participation+.

   +Including acute or chronic disease or medical condition that would place the subject at an unacceptable risk of injury, render the subject unable to meet the requirements of the protocol, or may interfere with the evaluation of responses or the subject's successful completion of this trial.

   These include:

   History of inflammatory bowel disease (IBD) (including ulcerative colitis, Crohn's disease, indeterminate colitis, or celiac disease). Within the past 12 months, has any of the following: irritable bowel syndrome (IBS) or any active uncontrolled gastrointestinal disorders or diseases as assessed by the investigator, including symptoms or evidence of active gastritis or gastroesophageal reflux disease, gastric surgery or gastric acid hyper-secretory disorders (e.g., Zollinger-Ellison syndrome), gastrointestinal obstruction, ileus, gastric retention, bowel perforation, toxic colitis, persistent infectious gastroenteritis, persistent or chronic diarrhea of unknown etiology, Clostridium difficile infection. History of immunodeficiency due to congenital or hereditary causes, underlying illness or treatment, autoimmune disorders, or chronic inflammatory disorders, refer to Appendix C. History of an inflammatory arthritis such as reactive arthritis, Reiter's syndrome, ankylosing spondylitis, rheumatoid arthritis, or GBS. Known active neoplastic disease^, a history of any hematologic malignancy, or have used anticancer chemotherapy/radiation therapy (cytotoxic) within 5 years prior to study vaccination. Other condition requiring daily therapy that would place the volunteer at

increased risk or AEs. Other laboratory abnormalities which in the opinion of the investigator precludes participation in the study. Clinically significant abnormalities on physical exam. ^non-melanoma, treated, skin cancers are permitted.

2. Documented history of auto-immune conditions in a first-degree relative. Examples include reactive arthritis, Reiter's syndrome, ankylosing spondylitis, rheumatoid arthritis, or GBS.
3. History of PIMMCs.
4. Evidence of inflammatory arthritis on exam and/or positive serology results for HLA-B27.
5. Positive HIV, Hepatitis B surface antigen (HBsAg), or Hepatitis C antibodies (HCVs).
6. Participation in a previous *Campylobacter* study or reports having received vaccination against *Campylobacter* within the last 3 years.
7. History of microbiologically confirmed *Campylobacter* infection in the last 3 years.
8. Occupation involving handling of *Campylobacter* bacteria or vaccine products currently or in the past 3 years.
9. Use of immunosuppressive/immunomodulating disease therapy within 90 days
10. Received Ig or other blood products (with exception of Rho D Ig) within 90 days prior to enrollment.
11. Have a history of severe reactions following previous immunization with any licensed or unlicensed vaccine.
12. Known hypersensitivity to any components of vaccine, adjuvant, or diluent.
13. Received or plan to receive a licensed live vaccine within 30 days prior to 1st vaccination and to 30 days after the last vaccination.
14. Received or plan to receive a licensed, inactivated, vaccine within 14 days prior to 1st vaccination to 14 days after the last vaccination, or a seasonal influenza and/or COVID-19 vaccine ± 7 days from study product vaccination.
15. Individuals in whom the ability to observe possible local reactions at the eligible injection sites (deltoid region) is unacceptably obscured due to a physical condition or permanent body art.
16. Within 14 days prior to vaccination has received an oral or parenteral (including intra-articular) corticosteroid of any dose for 5 or more days, or high-dose inhaled corticosteroids.
    a. High dose defined per age as using inhaled high dose per reference chart (https://www.nhlbi.nih.gov/files/docs/guidelines/asthma_qrg.pdf)
17. Current or history of alcohol or drug abuse within one year prior to enrollment.

18. Have any diagnosis, current or past, of schizophrenia, bipolar disease, or other psychiatric diagnosis that may interfere with subject compliance or safety evaluations.
19. Have been hospitalized for psychiatric illness, history of suicide attempt, or confinement for danger to self or others within one year prior to enrollment.
20. Are pregnant, breastfeeding, or plan to become pregnant or breastfeed at any given time during the study.
21. Have an acute illness as determined by study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator, within 72 hours prior to enrollment.
    a. An acute illness which is nearly resolved with only minor residual symptoms remaining is allowable if, in the opinion of a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator, the residual symptoms will not interfere with the ability to assess safety parameters as required by the protocol.
22. Received an investigational product within 30 days prior to the first study vaccination or expect to receive an investigational product during the study period.
    a. Including vaccine, drug, biologic, device, blood product, or medication, other than from participation in this trial.
23. Have abnormal screening laboratory values within 30 days prior to enrollment.
    a. Refer to Appendix B for range of normal laboratory values.
    b. Screening laboratory values that are outside acceptable range but are thought to be due to an acute condition or due to laboratory error may be repeated once. [see MOP]

4.1.3 Subject Qualification Criteria for Vaccinations 2, 3

If Halting Criteria in section 7.6 are met, further study vaccinations will be halted pending SRC and Safety Monitoring Committee (SMC) review.

Any subject with 1) a SAE assessed as related to the vaccine, or 2) a PIMMC regardless of vaccine relatedness criterion excluding subjects with a history of PIMMC, will be discontinued from study vaccinations.

Subsequent vaccinations may proceed if the following criteria are all answered yes:

1. Oral temperature less than 100.4°F.
2. Negative urine pregnancy test, as applicable.
3. Females of childbearing potential continue to agree to use acceptable contraception for the duration of the trial (including the safety communication follow up period).

4. Has not received or plans to receive a licensed, inactivated, vaccine within 14 days prior to 1st vaccination to 14 days after the last vaccination or a seasonal influenza and/or COVID-19 vaccine ± 7 days from study product vaccination.
5. Has not received or plans to receive a licensed live vaccine through 30 days after the last vaccination.
6. Within 14 days prior to vaccination has not received an oral or parenteral (including intra-articular) corticosteroids of any dose for 5 or more days, or high-dose inhaled corticosteroids.
    a. High dose defined per age as using inhaled high dose per reference chart (https://www.nhlbi.nih.gov/files/docs/guidelines/asthma_qrg.pdf
7. Has not had an acute illness as determined by study clinician licensed to make medical diagnoses and listed on the Form FDA 1572, within 72 hours prior to vaccination.
    a. An acute illness which is nearly resolved with only minor residual symptoms remaining is allowable if, in the opinion of the site PI or appropriate sub-investigator, the residual symptoms will not interfere with the ability to assess safety parameters as required by the protocol.
8. Has not had a new or prior unsolicited AE, unrelated to study product, that is more than Grade 2 at the time of vaccination.
9. Has not had a new unsolicited AE related to study product that is greater than Grade 1 at the time of vaccination.
10. Has not had a prior unsolicited AE related to study product persisting at the time of vaccination and is greater than Grade 1.
11. Has not had a new solicited AE related to study product that is greater than Grade 1 at the time of vaccination.
12. Has not had a prior solicited AE related to study product persisting at the time of vaccination and is greater than Grade 1.
13. In the judgement of the PI does not have any other contraindication to dosing.

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

4.2.1 Withdrawal from the Study or Discontinuation of the Study Product

Subjects may voluntarily withdraw their consent for study participation at any time without penalty or loss of benefits to which they are otherwise entitled.

An investigator may also discontinue a subject from receiving study product for any reason. Follow-up safety evaluations will be conducted if the subject agrees. If a subject discontinues

study product or is withdrawn from the study prior to completion, the reason for this decision must be recorded in the eCRFs.

The reasons for withdrawal or discontinuation of study product, might include, but are not limited to the following:

- Subject meets halting criteria
- Subject becomes noncompliant
- Disease or medical condition, or new clinical finding(s) for which continued participation, in the opinion of the investigator might compromise the safety of the subject, interfere with the subject's successful completion of this study, or interfere with the evaluation of responses
- Subject becomes lost to follow-up
- Subject becomes pregnant

The investigator should be explicit regarding study follow-up (e.g., safety follow-up) that might be carried out despite the fact the subject will not receive further study product. The alternate visit schedule and procedures pertaining to subjects withdrawn from study product will be further explained in the MOP. If the subject agrees, every attempt will be made to follow all AEs through resolution or stabilization.

The procedures that collect safety data for the purposes of research must be inclusive in the original informed consent or the investigator may seek subsequent informed consent using an IRB/IEC approved consent form with the revised procedures.

Investigator will inform the subject that already collected data will be retained and analyzed even if the subject withdraws or is discontinued from this study.

4.2.2 Handling of Withdrawals

In the case of subjects who are lost to follow-up, extensive effort (i.e., three documented contact attempts via phone calls, emails, text messages, etc., made on separate occasions and followed by a certified letter) will be made to locate or recall them, or at least to determine their health status. These efforts will be documented in the subject’s study records. Every attempt will be made to follow all AEs, including solicited local site and systemic AEs, unsolicited non-serious AEs, and SAEs, ongoing at the time of early withdrawal through resolution or stabilization as per applicable collection times defined for the specific type of AE.

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

4.2.3 Study Termination

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

5 STUDY PROCEDURES

Study Duration

It is projected that the length of the overall study, from initiating screening to the completion of the last safety communication follow up visit, will be approximately 24 months. This projection is based on the six sentinel subjects in each cohort and the assumption that vaccination of the next cohort will begin after the SRC has reviewed blinded safety data through the reactogenicity period post-3rd study vaccination in the previous cohort. Additionally, as the study is using a novel adjuvant, study participants will receive a final safety call approximately 1 year after receiving their final vaccination to assess for new onset AEs of special interest.

Duration of Individual Subject Participation

Participation for an individual subject will be approximately 15 months, which includes a 30-day screening period, vaccination at Day 1, 29, and 57, and active surveillance through 28 days after the 3rd dose of vaccine. Safety communication contacts will be made at 6 months and 1 year post final vaccination.

Study Schedule

Complete study schedule details listed by type of visit are described below. Refer also to Appendix A. Schedule of Events.

5.1 Screening

Day -30 to -2

The following activities will be performed at screening and may be done all at one visit or split into separate visits.

- Subjects will be provided with a description of this trial (purpose and study procedures) and asked to read and sign the ICF. The ICF will be signed prior to performing any study procedures, including any screening procedures.
- Demographic information will be obtained by interview of subjects.
- Eligibility criteria will be reviewed with subjects.

The following screening procedures will be completed to ensure that the potential subject is eligible for the study:

- Complete medical history will be obtained by interview of subjects, including current contraceptive history with females of childbearing potential and receipt of seasonal influenza and COVID-19 vaccines for all participants.
- History of all concomitant medications taken within 30 days prior to signing the ICF will be obtained by interview of subjects or abstraction from eCRF.
- Vital signs, including oral temperature, pulse, and BP, will be obtained. Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature.
- Height and weight will be collected for BMI calculation.
- An abbreviated physical examination will be performed to include the following organs and organ systems: general appearance, skin, head and neck, lungs, heart, liver, spleen, extremities, musculoskeletal and lymph nodes by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator. Breast, genito-urinary and rectal exams are not considered a routine part of the abbreviated physical exam.
- A urine pregnancy test will be performed on all females of childbearing potential and must be negative.
- Counsel on avoidance of pregnancy for females of childbearing potential.
- A urine dipstick will be performed for urine protein.
- A urine toxicology will be performed for opiates.
- A stool kit and collection instructions will be provided in anticipating for the expected sample at enrollment.
- Venous blood will be collected for screening laboratory tests. These include:
    - Hematology: WBC, absolute neutrophil count (ANC) hemoglobin (Hgb), and platelets (PLTs)
    - Chemistry: total bilirubin (T. bili), alanine aminotransferase (ALT), creatinine, sodium, potassium
    - Serology: HIV – 1/2 antibody, HCV, HBsAg, HLA-B27

Testing results must be confirmed to meet the eligibility criteria as outlined in the Inclusion / Exclusion Criteria prior to randomization. Acceptable screening laboratory values are those that fall within the normal ranges as listed in Appendix B.

- A low creatinine value or a low ALT value, as well as trace amounts of urinary protein, are acceptable for study inclusion.
- As they are not considered to be clinically significant, subjects with a Grade 1 abnormality may be re-screened once if there is a suspected inter-current, short-term medical illness or a suspected laboratory error.

If screening labs are collected more than 30 days before vaccination, the screening labs may be re-collected to determine if the subject remains eligible for study participation. No subject may be screened **more than twice due to a screening failure result as defined above.** The Study Sponsor and PI will be contacted for clarification or questions regarding screening failures. All eligibility criteria must be satisfied before a subject is enrolled.

A subject may also be re-screened if the subject was screened eligible for a previous cohort but was not enrolled (e.g., scheduling conflict, vacation).

Subjects will be informed of their screening test results by a member of the study team. Subjects will be encouraged to follow up with their primary care providers if results are of clinical significance or are sensitive in nature.

5.2 Enrollment/Baseline

Day 1, Visit 01

Subjects who pass screening and meet all the inclusion criteria and none of the exclusion criteria may be considered for study enrollment.

- Screening blood testing and study entry requirements will be reviewed with subjects prior to the first study vaccination to ensure subjects continue to qualify for vaccination. Laboratory results must be within acceptable parameters as outlined in the inclusion / exclusion criteria.
- Interim medical history, including an assessment for new medical conditions, stability of chronic diseases, MAAEs, NOCMCs and symptoms suggestive of PIMMCs, will be obtained by interview of subjects prior to study vaccination. Any changes in medical

history since the screening visit will be reviewed to ensure subjects continue to qualify for vaccination.

- All concomitant medications will be reviewed with subjects prior to study vaccination for accuracy and completeness. Any new concomitant medications will be reviewed to ensure subjects continue to qualify for vaccination.
- Vital signs, including oral temperature, pulse, and BP, will be obtained prior to study vaccination to ensure subjects continue to qualify for vaccination. Vital signs assessed on Day 1 prior to study vaccination will be considered as baseline. Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature.
- If indicated, a targeted physical examination may be performed prior to study vaccination.
- For all participants of childbearing potential, a urine pregnancy test will be performed within 24 hours of vaccination. Results must be negative and known prior to study vaccination.
- Pre-vaccination Reactogenicity assessments will be completed.
- Venous blood will be collected immediately prior to study vaccination for:
    - Serum for Serology
    - PBMC for ALS
    - PBMC for secondary research
    - Serum for secondary research
- Attempt to collect stool sample for future use. Every attempt should be made to collect sample from participant. Enrollment can continue in the rare case the sample cannot be collected.
- Subjects will be enrolled in Advantage eClinical® and randomly assigned to a treatment arm prior to study vaccination.
- Subjects will receive one dose of study vaccine via a single IM injection into the deltoid muscle of the subject's arm. It is strongly recommended the unblinded administrator administers the study product(s) into the subject's left deltoid. The site of injection and time of study vaccine administration to the subject will be recorded on the appropriate eCRF
- Subjects will be observed in the clinic for at least 30 minutes after study vaccination. The study vaccination site will be examined, post-administration reactogenicity assessments

will be performed, and any AE/SAEs will be recorded on the appropriate eCRF prior to discharge from the clinic.

- Subjects will be instructed how to complete their e-memory aid. Subjects will be provided with study-related materials (including a digital thermometer and measuring ruler) to record daily oral temperature and potential solicited injection site reactions. Subjects will be encouraged to take their oral temperature around the same time each day. Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature. Subjects will be instructed to notify the study center if they develop any severe reactions after study vaccination. If the site PI or appropriate sub-investigator deems the reaction severe enough, further instructions will be given to the subject on the proper course of action, including a return to the clinic for immediate evaluation if appropriate.
- Counsel on avoidance of pregnancy for females of childbearing potential.

5.3 Follow up Visits

Follow-up visits are scheduled in reference to most recent study vaccination date. See Appendix A. Schedule of Events.

5.3.1 Follow up: 3 Days (±1) and 15 Days (±2) following each vaccine

These visits may be performed in the clinic or virtually.

The following procedures as applicable, will occur.

- Interim medical history, including an assessment for new medical conditions, stability of chronic diseases, MAAEs, NOCMCs, and PIMMCs, will be obtained by interview of subjects and any changes since the previous visit will be noted.
- All concomitant medications will be reviewed with subjects and recorded on the appropriate eCRF.
- Vital signs, including oral temperature, pulse, and BP, will be obtained. Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature.
- A targeted physical examination may be performed if indicated based on review of complete medical history and any updates obtained by interview of subjects since the previous visit, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.

- All AE/SAEs will be recorded on the appropriate eCRF.
- The study vaccination site will be examined, except for visits 04, 08, and 12.
- E-Memory Aid information will be reviewed with subjects, except for visits 04, 08, and 12.
- Counsel on avoidance of pregnancy for females of childbearing potential.
- A stool kit and collection instructions will be provided in anticipation for the expected sample at the next visit, except for visits 04, 08 and 12.

5.3.2 Follow up: 7 Days (+1) after each vaccination

All procedures listed in section 5.3.1 as well as procedures listed below are to be performed unless exceptions are noted.

- Venous blood will be collected for:
    - WBC, Hgb, PLT, ANC, ALT, T. bili, creatinine, sodium, and potassium.
    - Serum for Serology
    - PBMC for ALS
    - PBMC for secondary research
    - Serum for secondary research
- E-Memory Aid information will be reviewed with subjects
- Attempt to collect stool sample.

5.3.3 Subsequent Vaccination Visits: Day 29 (+2) and Day 57 (+2)

All subjects in each cohort will return on Day 29 (Visit 05) and Day 57 (Visit 09) after vaccination 1 and undergo the following procedures:

- Qualification criteria for subsequent vaccination visits, will be reviewed prior to vaccination. Section 4.1.3
- Interim medical history, including an assessment for new medical conditions, stability of chronic diseases, MAAEs, NOCMCs and symptoms suggestive of PIMMCs, will be obtained by interview of subjects prior to study vaccination. Any changes in medical history since the screening visit will be reviewed to ensure subjects continue to qualify for vaccination.

- Concomitant medications will be reviewed with subjects prior to study vaccination for accuracy and completeness. Any new concomitant medications will be reviewed to ensure subjects continue to qualify for vaccination.
- Vital signs, including oral temperature, pulse, and BP, will be obtained prior to study vaccination to ensure subjects continue to qualify for vaccination. Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature.
- If indicated after review of subject history, a targeted physical examination may be performed prior to study vaccination.
- For all participants of childbearing potential, a urine pregnancy test will be performed within 24 hours of vaccination. Results must be negative and known prior to study vaccination.
- Pre-vaccination reactogenicity assessments will be completed
- Venous blood will be collected immediately prior to study vaccination for:
    - Serum for Serology
    - PBMC for secondary research
    - Serum for secondary research
- Subjects will receive one dose of study vaccine via a single IM injection into the deltoid muscle of the subject's arm. It is strongly recommended the unblinded administrator alternate the subject's arms for injections. The site of injection (right or left arm) and time of study vaccine administration to the subject will be recorded on the appropriate eCRF.
- Subjects will be observed in the clinic for at least 30 minutes after study vaccination. The study vaccination site will be examined, post-administration reactogenicity assessments will be performed, and any AE/SAEs will be recorded on the appropriate eCRF prior to discharge from the clinic.
- Subjects will be instructed how to complete their e-memory aid. Subjects will be provided with study-related materials to record daily oral temperature and potential solicited injection site reactions. Subjects will be encouraged to take their oral temperature around the same time each day. Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature. Subjects will be instructed to notify the study center if they develop any severe reactions after study vaccination. If the site PI or appropriate sub-investigator deems the reaction severe

enough, further instructions will be given to the subject on the proper course of action, including a return to the clinic for immediate evaluation if appropriate.

- Counsel on avoidance of pregnancy for females of childbearing potential.

5.3.4 Follow-up: Day 85 (±2) and Day 113 (±4)

All cohorts will return on Day 85 (Visit 13) and 113 (visit 14). The following procedures will be performed.

- Interim medical history, including an assessment for new medical conditions, stability of chronic diseases and symptoms, MAAEs, NOCMCs, and suggestive of PIMMCs, will be obtained by interview of subjects. Please note that AEs (new medical conditions) will be assessed for 28 days post last vaccination. SAEs will be followed throughout the study duration.
- Concomitant medications will be reviewed with subjects for accuracy and completeness. Only concomitant medications taken within 30 days of enrollment through 28 days post last vaccination are collected in Advantage eClinical®.
- Vital signs, including oral temperature, pulse, and BP, will be obtained. Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature.
- If indicated after review of subject history, a targeted physical examination may be performed.
- For all participants of childbearing potential, a urine pregnancy test will be performed.
- Counsel on avoidance of pregnancy for females of childbearing potential.
- Venous blood will be collected for:
    - Serum for Serology
    - PBMC for secondary research
    - Serum for secondary research

5.3.5 Safety Communication Follow Up, Day 240, 420 (±7)

Participants will be contacted to complete a safety assessment via phone or email communication 6 months and 1 year following the 3rd or final study vaccination. The safety assessment will

consist of inquiring about SAEs. MAAEs, NOCMCs, and symptoms suggestive of PIMMCs will be collected to satisfy outcome measures.

5.4 Unscheduled Study Visits

Subjects will be asked to notify the study staff promptly if they develop any illness. If the study staff determines the symptoms are potentially significant, the subject will be asked to come to the clinic for an evaluation. Subjects will be asked to complete an unscheduled visit for any event that warrants follow-up. All events will be followed to resolution or until determined to be stable.

5.4.1 Early Termination Visit

If the subject decides to withdraw consent after receiving investigational product and declines study duration follow up, it will be requested that the subject return for a final visit where follow-up safety evaluations will be conducted.

5.5 Protocol Deviations

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

These practices are consistent with ICH E6:

4.5 Compliance with Protocol, Sections 4.5.1, 4.5.2, and 4.5.3

5.1 Quality Assurance and Quality Control, Section 5.1.1

5.20 Noncompliance, Sections 5.20.1, and 5.20.2.

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

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

6 DESCRIPTION OF CLINICAL AND LABORATORY EVALUATIONS

6.1 Clinical Evaluations

Following consent, a screening evaluation will be performed. Refer to Appendix A: Schedule of Events, for clinical evaluation time point specifics. Refer to the MOP for clinical evaluation specifics.

Screening for eligibility will occur from Days -30 to -2 to determine health status of potential subjects. This will include the following clinical evaluations:

- A complete medical history
- Review of concomitant medications
- Height and weight will be collected
- Vital signs (heart rate (HR), BP, oral temperature)
- Abbreviated physical exam
- Collection of blood for screening laboratory testing
- Urine for toxicology
- Urine pregnancy test will be performed locally on all female subjects of childbearing potential and a positive result will exclude the subject from receipt of study product
- Urine dipstick for protein

Once screening eligibility has been verified, Day 1 vaccination will occur, and the enrollment period will begin. After enrollment, the following clinical evaluations will be performed.

- Vital signs (HR, BP, oral temperature)
- If indicated, a targeted physical examination may be performed prior to study vaccination.
- Interim medical history
- MAAE, NOCMC and PIMMCs assessments
- Review of concomitant medications
- A urine pregnancy test will be performed locally on all female subjects of childbearing potential and a positive result will exclude the subject from receipt of study product.
- Collection of blood for baseline and safety laboratory testing

- Local and systemic symptom assessment using e-memory aid. Subjects will be followed for 7 days post-vaccine (through Study Day 8)
- Safety follow up visits via phone or email communication

6.1.1 Research Procedures

Refer to Appendix A: Schedule of Events, for time point specifics. Refer to section 6.2.2 for testing specifics.

- E-memory aid review to validate the reactogenicity severity scores
- Collection of blood
- Collection of stools

6.1.2 Assessment of Concomitant Medications/Treatments other than Study Product

- Administration of any medications or non-study vaccines will be documented in the appropriate eCRF. All concomitant medications, taken in the 30 days prior to study enrollment through 28 days following last vaccination or early termination, whichever occurs first, will be recorded. All concomitant medications associated with SAEs, MAAEs, NOCMCs, and PIMMCs through the assessment period for these events will be recorded.
- All prescription and over-the-counter medications as well as vitamins and supplements will be recorded.

Assessment of eligibility also will include a review of permitted and prohibited medications (per the exclusion criteria).

Use of new medications should prompt evaluation for the presence of an AE or new chronic medical condition.

Medications which may interfere with the evaluation of the investigational product should not be used unless absolutely necessary. Medications or treatments which are prohibited are listed in the exclusion criteria.

6.1.3 Assessment of Subject Compliance with Study Intervention/Investigational Product/Investigational Device

Subjects will be directly observed at the time of dosing by a member of the clinical research team who is delegated to administer the study product. Administration will be documented in the appropriate eCRF.

6.2 Laboratory Evaluations

6.2.1 Clinical Laboratory Evaluations

Safety laboratory evaluations will be performed by the local lab of the performance site.

Clinical safety lab testing will include hematology and chemistry.

Hematology: WBC, ANC, Hgb, and platelet count

Chemistry: sodium, potassium, creatinine, ALT, and T. bili

For females of childbearing potential, urine pregnancy testing will be performed in the clinic by a qualified study team member using a commercially available test at screening, Days 85 and 113, and within 24 hours before each vaccination. Pregnancy test results must be negative for subjects to be eligible for enrollment and to be qualified to receive vaccination.

Subjects will be tested for HLA-B27, HIV, HBsAg, and antibody to Hepatitis C at screening only.

Urinalysis will be done to test for urine protein via dipstick in the clinic at screening only. A clean-catch, mid-stream urine specimen will be collected in a sterile urine cup.

Urine test for opiates: A clean-catch, mid-stream urine specimen will be collected in a sterile urine cup and transported to the clinical laboratory for processing and examination at screening only.

6.2.2 Research Assays

Serology:
At times specified in the protocol and the MOP, blood will be collected for IgG and IgM assay by enzyme-linked immunosorbent assay (ELISA). The serum will be separated and stored frozen for determination of specific antibody responses against *C. jejuni* capsule and CRM_{197} antigens.

Antibody in Lymphocyte Supernatant (ALS):
At times specified in the protocol and the MOP, the PBMCs will be isolated from whole blood and cryopreserved to be used in ALS assays. The ALS assay will measure by ELISA the secretion of *C. jejuni* capsule specific antibodies in cultures of PBMCs.

Secondary Research:

In addition to Research Assays listed above, serum, stool and PBMCs will be preserved for secondary research. Details of assays, methodology and location of testing will be determined under a separate research protocol yet to be determined.

- **Serum**
  Blood for serum samples at days specified in the protocol will be collected, processed, and stored at -70°C until used for secondary research.

- **Stool**
  A stool sample (4-5gm) will be placed in a 30 mL Oakridge tube and frozen at -70ºC or colder until used for secondary research.

- **PBMCs**
  The PBMCs will be isolated from whole blood and cryopreserved until used for secondary research.

6.2.2.1 Laboratory Specimen Preparation, Handling, and Storage

Biosamples (serum, stools, and PBMCs) for immunological assays will be collected, processed, cryopreserved, and stored as detailed in the protocol MOP. All immunological assays will be performed in batches after all samples have been collected for a given assay within a cohort.

6.2.2.2 Laboratory Specimen Shipping

Instructions for specimen preparation, handling, storage, and shipment as applicable are included in the protocol-specific MOP.

7 ASSESSMENT OF SAFETY

7.1 Assessing and Recording Safety Parameters

This will be the first time that the CJCV2 vaccine (either alone or in combination with ALFQ) has been administered to humans. However, in a phase 1 clinical trial, CJCV1, the initial *Campylobacter*-CCV (co-administered with and without AH) was administered safely to 48 human subjects in a 2-dose series (days 1 and 29). Across all cohorts of the study, the vaccine was well-tolerated with self-limited, post-vaccination AEs limited to mild severity without a clear increase in frequency upon dose escalation. Vaccine site reactions were most common when the AH adjuvant was co-administered. There were no AEs that met study stopping criteria.

Both MPLA and QS-21 have been safely given to human subjects in multiple clinical trials in combination with multiple candidate vaccines against diverse diseases, including hepatitis B, malaria, varicella-zoster virus, and tuberculosis. Though significant safety events are not anticipated, they will be closely monitored as data are limited using 3D-PHAD® and QS-21 together.

Safety will be assessed by the frequency and severity of solicited and unsolicited AEs.

7.1.1 Adverse Events (AEs)

ICH E6 defines an AE as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, regardless of its causal relationship to the study treatment. FDA defines an AE as any untoward medical occurrence associated with the use of a drug in humans, whether considered drug related.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study recipient presenting for medical care, or upon review by a study monitor.

All AEs, including solicited local (injection site) and systemic (subjective and quantitative) reactions, will be captured on the appropriate eCRF. Information to be collected for AEs includes event description, date of onset, and assessment of severity, relationship to study product and alternate etiology (assessed only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as an investigator/sub-investigator), date of resolution, seriousness,

and outcome. AEs occurring during the trial collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the severity of any pre-existing medical condition increases, it should be recorded as an AE.

7.1.1.1 Adverse Events Grading

All AEs (laboratory and clinical symptoms) will be graded for severity and assessed for relationship to study product (see definitions). AEs characterized as intermittent require documentation of onset and duration of each episode. The start and stop date of each reported AE will be recorded on the appropriate eCRF. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of intensity.

Severity of Event:

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

- Mild (Grade 1): Events that are usually transient and may require only minimal or no treatment or therapeutic intervention and generally do not interfere with the subject's usual activities of daily living.
- Moderate (Grade 2): Events that are usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe (Grade 3): Events interrupt usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. Severe events are usually incapacitating.

Relationship to Study Product: The assessment of the AE's relationship to study product will be done by the study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator. Whether the AE is related or not, is not a factor in determining what is or is not reported in this trial. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

In a clinical trial, the study product must always be suspect. The relationship to study product will be assessed for AEs using the terms related or not related:

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

7.1.2 Reactogenicity

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

Table 3: Injection Site Reactogenicity Grading

Injection Site Reaction	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Pain – experienced without touching the injection site (spontaneous discomfort)	Subject is aware of pain, but it does not interfere with daily activity, **and** if pain medication is used, it is Over the Counter (OTC) and used for less than 24 hours	Subject is aware of pain; there is interference with daily activity **or** OTC pain medication is used for more than 24 hours	Subject is aware of pain, **and** it prevents daily activity or pain requires prescription medication
Tenderness-experienced with touching the injection site	Subject is aware of pain, but it does not interfere with daily activity, **and** if pain medication is used, it is Over the Counter (OTC) and used for less than 24 hours	Subject is aware of pain; there is interference with daily activity **or** OTC pain medication is used for more than 24 hours	Subject is aware of pain, **and** it prevents daily activity or pain requires prescription medication
Ecchymosis (Bruising)*	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
Erythema (Redness)*	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity

Injection Site Reaction	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Induration (Hardness)/Edema (Swelling)*	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity

* Will also be measured in mm but size will not be used as halting criteria.

Ecchymosis, erythema, and induration/edema as analyzed by measurement will be graded as follows:

Table 4: Injection Site Reactogenicity Measurements

Injection Site Reaction	Small	Medium	Large
Ecchymosis (Bruising)*	<20 mm	20 mm – 50 mm	>50 mm
Erythema (Redness)*	<20 mm	20 mm – 50 mm	>50 mm
Induration (Hardness)/Edema (Swelling)*	<20 mm	20 mm – 50 mm	>50 mm

* Will not be used as halting criteria.

Table 5: Subjective Systemic Reactogenicity Grading

Systemic (Subjective)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Feverishness	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Fatigue	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Malaise	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Myalgia*	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity

Systemic (Subjective)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Arthralgia*	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Headache	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity or headache requires prescription medication
Nausea	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity or nausea requires prescription medication
Vomiting	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity or vomiting requires prescription medication

* Not at injection site.

Table 6: Quantitative Systemic (Oral Temperature) Reactogenicity Grading

Systemic (Quantitative)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Fever* – oral†	38.0°C – 38.4°C 100.4°F – 101.1°F	38.5°C – 38.9°C 101.2°F – 102.0°F	>38.9°C >102.0°F

† Oral temperature assessed on Day 1 prior to the first study vaccination will be considered as baseline.

* A fever can be considered not related to the study product if an alternative etiology can be documented.

† Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature.

7.1.3 Serious Adverse Events (SAEs)

An AE or suspected adverse reaction is considered a SAE if, in the view of either the site PI or sponsor, it results in any of the following outcomes:

- death,

- a life-threatening adverse event[1],
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- a congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalizations may be considered serious when, based upon appropriate medical judgment they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

[1] Life-threatening adverse event. An AE is considered "life-threatening" if, in the view of either the site PI or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 or by the Institution as the site PI or Sub-Investigator.
- Recorded on the appropriate SAE eCRF.
- Followed through resolution by a licensed study physician (for IND studies, a physician listed on the Form FDA 1572 as the site PI or Sub-Investigator).
- Reviewed and evaluated by DMID, SMC (periodic review unless related), and the IRB/IEC.

7.2 Specification of Safety Parameters

Safety will be assessed by the frequency and severity of the solicited and unsolicited AEs.

7.2.1 Solicited Events

Solicited Events are AEs that are common and known to or expected to occur following the administration of the study product. Subjects will be assessed for AEs following vaccination

administration and will complete an e-memory aid to record symptoms for 7 days following each vaccination. The subjects will be provided with a thermometer. The subject e-memory aid will be reviewed with the subject at subsequent visits. Any symptoms still present after the solicited event collection period (Day 8 post vaccination doses) will continue to be followed until resolution or determined to be stable per investigator.

- Solicited (local injection site) events listed for this protocol include pain, tenderness, ecchymosis, erythema, and induration/edema.
- Solicited (systemic) events listed in this protocol include fever (elevated temperature), feverishness, fatigue, malaise, myalgia, arthralgia, headache, and nausea.

7.2.2 Unsolicited Events

Unsolicited event(s), including MAAEs, NOCMCs, PIMMCs, and SAEs, that occur following administration of vaccination doses will be collected from subjects throughout their period of participation in the study. Unsolicited AEs will be followed until resolution or determined to be stable per investigator discretion. A summary of unsolicited AEs will be included as part of the clinical study report (CSR).

7.2.3 New-Onset Chronic Medical Conditions (NOCMCs)

NOCMCs are defined as any new ICD-10 diagnosis that is applied to the subject during the duration of the study, after receipt of the study agent, that is expected to continue for at least 3 months and requires continued health care intervention.

7.2.4 Medically Attended Adverse Events (MAAEs)

For each unsolicited AE experienced, the subject will be asked if he/she had received medical attention, defined as hospitalization, an ER visit, or an otherwise unscheduled visit to or from medical personnel for any reason. AEs characterized by such unscheduled medical care will be designated as MAAEs.

7.2.5 Potentially Immune-Mediated Medical Conditions (PIMMCs)

PIMMCs constitute a group of AEs that includes diseases which are clearly autoimmune in etiology and other inflammatory and/or neurologic disorders which may or may not have autoimmune etiologies. PIMMCs currently in effect are presented in Appendix C: List of PIMMCs.

7.2.6 Suspected Unexpected Serious Adverse Reactions (SUSAR)

A SUSAR is an adverse event reaction that meets all three of the following criteria:

- Serious and
- Unexpected and
- At least possibly related to the study product.

Unexpected event means an event unforeseen by the researcher or the participant, in terms of nature, severity, or frequency, and is not listed in the IB, package insert, and/or summary of product characteristics.

7.2.7 Dose Escalation Criteria

7.2.7.1 Cohort Studies

The period from when the first sentinel subjects are vaccinated through seven days after the last sentinel subject was vaccinated will be reviewed. If no safety issues are noted, the remaining subjects in the cohort will be vaccinated. If issues are noted, an ad hoc SMC meeting may occur to potentially review unblinded data to decide if the remaining subjects in the cohort will be vaccinated.

Prior to dose escalation, the SRC will review the study data and provide guidance on proceeding to the next dose level. The dose escalation data reviews will include blinded data, but if necessary for safety considerations, the SMC will have access to unblinded data.

7.3 Reporting Procedures

7.3.1 Reporting Serious Adverse Events

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

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

DMID Pharmacovigilance Group
Clinical Research Operations and Management Support (CROMS)

[redacted]
Bethesda, MD 20817, USA
SAE Hot Line: [redacted]
SAE FAX Number: [redacted]
SAE Email Address: [redacted]

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

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

The site will send a copy of the SAE report. The DMID Medical Monitor and DMID Clinical Project Manager will be notified of the SAE by the DMID Pharmacovigilance Group. The DMID Medical Monitor will review and assess the SAE for regulatory reporting and potential impact on study subject safety and protocol conduct.

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

7.3.2 Regulatory Reporting for Studies Conducted Under DMID-Sponsored IND

Following notification from the site PI or appropriate sub-investigator, DMID, as the IND sponsor, will report any suspected unexpected serious adverse reaction (SUSAR) and any SAEs related to study products to the FDA and will notify all site PI's (i.e., all PI's to whom the sponsor is providing drug) under its IND(s) or under any PI's IND(s) of potential serious risks from clinical studies or any other source, as soon as possible. DMID will report to the FDA any SUSAR and related SAEs that are fatal or life-threatening as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. If the related SAE is not fatal or life-threatening the IND safety report will be submitted within 15 calendar days after the sponsor determines that the information qualifies for reporting as specified in 21 CFR Part 312.32. Relevant follow up information to an IND safety report will be submitted as soon as the information is available. Upon request from FDA, DMID will submit to the FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

All SAEs designated as "not related" to study product(s), will be reported to the FDA at least annually in a summary format.

7.3.3 Reporting of Pregnancy

Pregnancy is not an AE but is a collectible event. Pregnancies occurring in study subjects will be reported in IDES (internet data entry system). With the subject's permission, all study mandated samples will be collected, and the subject will continue in follow-up for safety events. Efforts will be made to follow all pregnancies reported during the study to pregnancy outcome with the subject's permission.

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

All adverse and serious adverse events will be followed to resolution or until determined to be stable.

AEs will be assessed and followed from initial recognition of the AE through end of the protocol defined follow-up period.

SAEs will be followed up through resolution even if duration of follow-up goes beyond the protocol-defined the follow-up period.

Resolution of an AE is defined as the return to pre-treatment status or stabilization of the condition with the expectation that it will remain chronic.

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

The site PI or appropriate sub-investigator is responsible for recording all AE/SAEs that are observed or reported during this trial, regardless of the relationship to study product. AE/SAEs, abnormal laboratory test values, or abnormal clinical findings will be collected, assessed, documented, reported, and followed appropriately. Grading of the laboratory AEs will be based on the toxicity table.

7.6 Halting Rules

7.6.1 Sentinel Halting Criteria

Sentinel subject safety data (from day 1 of the dosing of the first Sentinel through day 7 post-dosing of the last Sentinel, for every dose) will be reviewed. Further study enrollment and dosing will be halted for SMC review/recommendation if any Halting Rules (listed below) are met from the time of the first study vaccination through the end of the first reactogenicity period (Day 8) at any dose for any sentinel participant.

- Death of an enrolled subject or any SAE if the SAE is considered related to the investigational products.
- Any Grade 3 unsolicited AE related to the investigational products.
- Any Grade 3 solicited AE. The size (as measured in mm) of erythema, ecchymosis, and induration/swelling will not be used as a halting criterion.

7.6.2 Cohort Halting Rules

Further study enrollment and dosing will be halted for SMC review/recommendation if any of the following Halting Rules are met after administration of any dose of study product within a cohort.

- Death of an enrolled subject or any SAE that is considered by the Medical Monitor to be related to the investigational products.
- Two (2) or more subjects in the same cohort experience the same or similar Grade 3 unsolicited AE (including but not limited to the same parameter or next level of coding in the Medical Dictionary for Regulatory Activities (MedDRA) hierarchy, High Level Term per the MedDRA current version) related to the investigational products.
- Two (2) or more subjects in the same cohort experience the same Grade 3 solicited AE. The size (as measured in mm) of erythema, ecchymosis, and induration/swelling will not be used as a halting criterion.

In the case of a halting rule being met due to Grade 3 solicited AEs in the CJCV2+adjuvant group, the cohort could proceed with CJCV2 alone for the following or remaining of the Cohorts (Cohorts 2 and/or 3) after review of the SMC.

7.6.3 Study Halting Criteria

Further study enrollment and dosing will be halted for SMC review/recommendation if any of the following Halting Rules are met after administration of any dose of study product.

- Death of an enrolled subject or any SAE if the SAE is considered by the Medical Monitor to be related to the investigational products.

- Three (3) or more subjects experience the same or similar Grade 3 unsolicited AE (including but not limited to the same parameter or next level of coding in the MedDRA hierarchy, High Level Term per the MedDRA current version) related to the investigational products.

  Three (3) or more subjects experience the same Grade 3 solicited AE. The size (as measured in mm) of erythema, ecchymosis, and induration/swelling will not be used as a halting criterion

If a halting rule is met, a thorough review of the event will be undertaken by the investigators and the SMC. Vaccination may be resumed with the concurrence of the SMC, sponsor's representative, and the PI.

The study may also be suspended because of safety findings such as an overall pattern of symptomatic, clinical, or laboratory events that the Medical Monitor considers related to the study products and that may appear minor in terms of individual events, but that may collectively represent a serious potential concern for safety

7.6.4 Individual Halting Criteria

A subject may be removed from the study if an investigator or medical monitor deems it in the best interest of the subject. A subject also may halt (discontinue participation) at any time. If a subject meets an individual halting criterion, it will not halt the study but halt the subject's involvement.

7.7 Safety Oversight by SMC

Safety oversight will be conducted by a Safety Monitoring Committee (SMC) which is an independent group of experts that advises the DMID. The primary responsibility of the SMC is to monitor subject safety. The SMC is external to the DMID and comprises at least 3 voting members. The SMC will consist of members with appropriate phase 1 study expertise to contribute to the interpretation of the data from this trial. Its activities will be delineated in a SMC charter that will describe the membership, responsibilities, and the scope and frequency of data reviews. The SMC will operate on a conflict-free basis independently of the study team. The DMID or the SMC may convene ad hoc meetings of the SMC according to protocol criteria or if there are concerns that arise during the study.

As defined in the charter, the SMC will meet before the initiation for the study and ad hoc as required due to occurrence of a safety event when a halting rule is met or for immediate concerns regarding observations during this study.

8 HUMAN SUBJECTS PROTECTION

8.1 Institutional Review Board/Independent Ethics Committee

The site PI will obtain IRB approval for this protocol to be conducted at his/her research site(s) and send supporting documentation to the DMID before initiating recruitment of subjects. The investigator will submit applicable information to the IRB/IEC on which it relies for the review, to conduct the review in accordance with 45 CFR 46, ICH E6 GCP, and as applicable, 21 CFR 56 (Institutional Review Boards) and 21 CFR 50 (Protection of Human Subjects), other federal, state, and local regulations. The IRB/IEC must be registered with OHRP as applicable to the research. DMID must receive the documentation that verifies IRB/IEC-approval for this protocol, associated informed consent documents, and upon request any recruitment material and handouts or surveys intended for the subjects, prior to the recruitment and enrollment of subjects.

Any amendments to the protocol or consent materials will be approved by the IRB/IEC before they are implemented. IRB/IEC review and approval will occur at least annually throughout the enrollment and follow-up of subjects and may cease if annual review is no longer required by applicable regulations and the IRB/IEC. The investigator will notify the IRB/IEC of deviations from the protocol and reportable SAEs, as applicable to the IRB/IEC policy.

Each institution engaged in this research will hold a current FWA issued by the OHRP for federally funded research.

Informed Consent Process

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continuing throughout the individual's trial participation. Before any study procedures are performed, informed consent will be obtained and documented. Subjects will receive a concise and focused presentation of key information about the clinical trial, verbally and with a written consent form. The explanation will be organized and presented in lay terminology and language that facilitates understanding why one might or might not want to participate.

An investigator or designee will describe the protocol to potential subjects face-to-face. The key information about the purpose of the study, the procedures and experimental aspects of the study, risks and discomforts, any expected benefits to the subject, and alternative treatment will be presented first to the subject.

Subjects will also receive an explanation that the trial involves research, and a detailed summary of the proposed study procedures and study interventions/products. This will include aspects of the trial that are experimental, the probability for random assignment to treatment groups, any expected benefits, all possible risks (including a statement that the particular treatment or procedure may involve risks to the subject or to the embryo or fetus, if the subject is or may become pregnant, that are currently unforeseeable), the expected duration of the subject's participation in the trial, alternative procedures that may be available and the important potential benefits and risks of these available alternative procedures.

Subjects will be informed that they will be notified in a timely manner if information becomes available that may be relevant to their willingness to continue participation in the trial. Subjects will receive an explanation as to whether any compensation and any medical treatments are available if injury occurs, and, if so, what they consist of, or where further information may be obtained. Subjects will be informed of the anticipated financial expenses, if any, to the subject for participating in the trial, as well as any anticipated prorated payments, if any, to the subject for participating in the trial. They will be informed of whom to contact (e.g., the investigator) for answers to any questions relating to the research project.

Information will also include the foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated. The subjects will be informed that participation is voluntary and that they are free to withdraw from the study for any reason at any time without penalty or loss of benefits to which the subject is otherwise entitled.

The extent of the confidentiality of the subjects' records will be defined, and subjects will be informed that applicable data protection legislation will be followed. Subjects will be informed that the monitor(s), auditors(s), IRB, NIAID, and regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations, and that, by signing a written ICF, the subject is authorizing such access.

Subjects will be informed that records identifying the subject will be kept confidential, and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available and, if the results of the trial are published, the subject's identity will remain confidential. Subjects will be informed whether private information collected from this research and/or specimens will be used for additional research, even if identifiers are removed.

Subjects will be allowed sufficient time to consider participation in this research trial and can discuss this trial with their family, friends, or legally authorized representative, or think about it prior to agreeing to participate.

ICFs will be IRB-approved, and subjects will be asked to read and review the consent form. Subjects must sign the ICF prior to starting any study procedures being done specifically for this trial.

Once signed, a copy of the ICF will be given to the subject(s) for their records. The subject(s) may withdraw consent at any time throughout the course of the trial. The rights and welfare of the subject(s) will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Study personnel may employ recruitment efforts prior to obtaining study consent if a patient-specific screening consent is on record or if the IRB has agreed that chart review is allowed without a fully executed screening consent. In cases where there is not a patient-specific screening consent on record, site clinical staff may pre-screen via chart review and refer potential subjects to the Research staff. Research staff would obtain written consent per the standard informed consent process before conducting protocol-specific screening activities.

New information will be communicated by the site PI to subjects who consent to participate in this trial in accordance with IRB requirements. The informed consent document will be updated, and subjects will be re-consented per IRB requirements, if necessary. Subjects will be offered a copy of all ICFs that they sign.

8.2 Consent for Secondary Research of Stored Specimens and Data

Subjects who consent to the study will have additional blood and stool collected for future use of remaining specimens. Collection of future use samples during the course of the study will help facilitate follow-on analyses, if warranted, to provide more comprehensive scientific insights into the impact (safety and immunological) of the vaccine on the host response to vaccination. It is important that extra blood and stool collection for future use be included in as many subjects as possible, due to the limited sample size.

Any remaining samples will be maintained for possible use in future research studies, such as examining additional immunological assessments or testing for antibodies against *Campylobacter* or other enteric vaccine development. These samples may be shared for purposes other than per protocol analysis with investigators at the participating VTEU site and with other investigators at other institutions once the CSR has been finalized.

Exact studies for which the stored specimens will be used have not been determined, but may include immune assay development, assessing innate immune factors, cytokines, and other evaluations.

The stored samples will be labeled with barcodes to maintain confidentiality. Research with identifiable samples and data may occur as needed, however, subject confidentiality will be maintained as described for this protocol and with IRB approval.

Samples will not be sold for commercial profit. Although the results of any future research may be patentable or have commercial profit, subjects will have no legal or financial interest in any commercial development resulting from any future research.

There are no direct benefits to the subject for extra specimens collected or from the secondary research. No results from secondary research will be entered into the subject's medical record. Incidental findings will not be shared with the subject, including medically actionable incidental findings, unless required by law.

Risks for loss of privacy and confidentiality are described below.

Remaining and future use research samples will be stored indefinitely at a NIH-designated research storage facility. These samples will not be sold or used directly for production of any commercial product. Each sample will be encoded (labeled) only with a barcode and a unique tracking number to protect subject confidentiality. There are no benefits to subjects in the collection, storage, and subsequent use of their specimens for future research. Reports about future research done with subjects' samples will NOT be kept in their health records.

Subjects may withdraw consent to future use samples at any time. They will need to contact the study site and the samples will be removed from the study repository after this study is completed and documentation will be completed. However, any data from a previously collected sample prior to the withdrawn consent will not be removed. Subjects who withdraw consent before the last visit will not have the extra blood drawn for future use.

Human Genetic Testing

Though there are no current plans for genetic testing, the research staff will seek the subjects' consent for genetic research in this study. The rights and privacy of human subjects who participate in genomic or phenotypic research studies will be protected at all times.

The consent process will include an explanation of the potential risks to the individual subjects and their families associated with data submitted to a NIH data repository and subsequent sharing. Data that may potentially identify human subjects will not be released in unrestricted databases. Subjects will be informed that the evolution of genomic technology and analytical methods raises the risk of re-identification, even when specimens are de-identified. The consent will include whether individual subject data will be shared through a NIH controlled access data repository. Data for genomic or phenotypic research will be submitted to a controlled access data repository, therefore, informed consent permitting the data sharing must be documented, even if the specimens are de-identified.

8.3 Exclusion of Women, Minorities, and Children (Special Populations)

As this is a Phase 1, first-in-human study, enrollment will be limited to males and non-pregnant/non-lactating females between 18 and 50 years of age, inclusive, at the time of enrollment. Special populations, e.g., non-English speakers, children, illiterate or non-writing individuals and vulnerable populations will not be enrolled in this study.

8.4 Subject Confidentiality

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality includes documentation, investigation data, subject's clinical information, and all other information generated during participation in the study. No information concerning the study, or the data generated from the study will be released to any unauthorized third party without prior written approval of the DMID and the subject. Subject confidentiality will be maintained when study results are published or discussed in conferences. The study monitors or other authorized representatives of the sponsor or governmental regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

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

Each subject will be assigned a unique study identifier. All eCRFs will identify the subject by a unique identifier, and the date. Names will not be used on any samples or in any publication of this study.

All efforts will be made by staff to protect the privacy of subjects, in accordance with the laws. These restrictions do not apply to: (1) information which becomes publicly available through no fault of the site PI or other study personnel; (2) information which is necessary to disclose in confidence to an IRB solely for the evaluation of the study; (3) information which it is necessary to disclose in order to provide appropriate medical care to a study subject; or (4) study results which may be published.

8.5 Certificate of Confidentiality

To protect privacy, we have received a Certificate of Confidentiality. With this Certificate, the researchers cannot be forced to release information that may identify the research subject, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify the subject, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects, like this study, or for information that must be released in order to meet the requirements of the Federal FDA.

A Certificate of Confidentiality does not prevent the subject from voluntarily releasing information about themselves or their involvement in this research. If any person or agency obtains a written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

The Certificate of Confidentiality does not prevent the researchers from reporting without the subject's consent, information that would identify the subject as a participant in the research project regarding matters that must be legally reported including child and elder abuse, sexual abuse, or wanting to harm themselves or others.

The release of individual private information or specimens for other research will only occur if consent was obtained from the individual to whom the information, document, or biospecimen pertains, *or* for the purposes of other research that is in compliance with applicable Federal regulations governing the protection of human subjects in research.

8.6 Costs, Subject Compensation, and Research Related Injuries

There is no cost to subjects for the research tests, procedures, and study product while taking part in this trial. Procedures and treatment for clinical care may be billed to the subject, subject's insurance or third party. Subjects may be compensated for their participation in this trial. Compensation will be in accordance with the local IRB's policies and procedures, and subject to IRB approval.

If it is determined by the site PI that an injury occurred to a subject as a direct result of the tests or treatments that are done for this trial, then referrals to appropriate health care facilities will be provided to the subject. Study personnel will try to reduce, control, and treat any complications from this trial. Immediate medical treatment may be provided by the participating site. No financial compensation will be provided to the subject by the NIAID, NIH to the subject, or by the participating site for any injury suffered due to participation in this trial.

9 STATISTICAL CONSIDERATIONS

9.1 Study Hypotheses

This study, like other Phase 1 studies, is exploratory rather than confirmatory, and thus is not designed to formally test any hypotheses. Rather the study is designed to assess the safety and immune responses of a range of doses of the CJCV2 vaccine administered with and without the adjuvant ALFQ.

9.2 Sample Size Considerations

We plan to enroll 60 subjects (20 per group). The sample size for each cohort was chosen based on the number of participants deemed appropriate for a first-in-human Phase 1 study. Given the small number of subjects per group, the precision of our estimate for AEs is limited. For example, using an exact binomial interval for no observed AEs within the 10 subjects per group yields a 95% confidence interval (CI) of 0-31% (Clopper-Pearson). Follow-on studies evaluating seemingly safe and immunogenic doses will be required with larger numbers of volunteers in order to better define the safety profile.

9.3 Treatment Assignment Procedures

9.3.1 Randomization Procedures

Per International Council for Harmonisation (ICH) guideline E6: GCP, screening records will be kept at the VTEU site to document the reason why an individual was screened, but failed trial entry criteria. The reasons why individuals failed screening will be recorded in the SDCC Advantage eClinical® (Electronic Data Capture System). Once consented and upon entry of demographic data and confirmation of eligibility for this trial, the subject will be enrolled. Subjects will be assigned randomly using permuted blocks to receive three IM doses of either CJCV2 (1 µg in Cohort 1, 3 µg in Cohort 2, or 10 µg in Cohort 3) vaccine alone or CJCV2 vaccine + ALFQ (200 µg 3D-PHAD® and 100 µg QS-21 in all Cohorts) adjuvant. The randomization scheme for this study is listed below and presented in **Table 1**. Subjects will be randomized such that the first six subjects of each cohort will be allocated to each of the two treatment arms as the sentinel group.

- CJCV2 alone group (N=30, 10 per cohort) will receive three-doses of CJCV2 vaccine + diluent administered by IM on Days 1, 29, and 57.
- CJCV2 + ALFQ group (N=30, 10 per cohort) will receive three-doses of CJCV2 vaccine + ALFQ adjuvant administered by IM on Days 1, 29, and 57.

Enrollment of subjects will be done online using the enrollment module of Advantage eClinical®.

The randomization code will be prepared by statisticians at the SDCC and included in the enrollment module for this trial. Advantage eClinical® will assign each subject to a group after the demographic and eligibility data have been entered into the system. A designated individual at the site will be provided with a code list for emergency unblinding purposes, which will be kept in a secure place. Instructions for use of the enrollment module are included in the Advantage eClinical® User's Guide. Manual back-up procedures and instructions are provided for use if the site temporarily loses access to the Internet, or the online enrollment system is unavailable.

9.3.2 Masking Procedures

This is a double-blind study. The CJCV2 vaccine with or without ALFQ will be prepared by the unblinded site pharmacist and will be administered by an unblinded vaccinator. Vaccination will be the only activity performed by the unblinded vaccinator. The unblinded vaccinator will transport the prepared vaccination in a dark colored UV split top bag to maintain the blind. Subjects, investigators, study personnel performing any study-related assessments following study vaccine administration, and laboratory personnel performing antibody assays will be blinded to whether the subject received CJCV2 alone or CJCV2+ALFQ.

The randomization scheme will be generated by the SDCC and provided to unblinded study personnel performing study vaccination preparations.

The SMC may receive data in aggregate and presented by treatment group, but without the treatment group identified. The SMC may be unblinded to individual study treatment assignments of subjects, as needed to adequately assess safety issues. The SRC may be unblinded to individual study treatment assignments of sentinel subjects only, as needed to adequately assess safety before proceeding to enroll non-sentinel subjects. Refer to the MOP for unblinding procedures.

9.3.3 Interim Safety Review

No formal statistical interim analysis based on the safety data is planned. The SRC will review safety data through seven days after the last sentinel subject is vaccinated before proceeding to vaccinate additional subjects in each cohort. The SRC will review safety data, which may include solicited and unsolicited AE/SAEs, concomitant medications, clinical laboratory values, vital signs, and any physical examinations, through Day 64 for each cohort prior to dose escalation.

9.3.4 Interim Immunogenicity Review

No interim immunogenicity review is planned.

9.4 Final Analysis Plan

A formal Statistical Analysis Plan (SAP) will be developed and finalized prior to unblinding for the final analysis, or database lock.

The final analysis will be performed, and CSR completed and distributed when all primary, secondary, and exploratory endpoint data are available

9.4.1 Analysis Populations

The Safety Population includes all subjects who received at least one dose of study vaccination.

The Modified Intent-to-Treat (mITT) Population consists of all subjects who received any study product and contributed both pre- and at least one post-study vaccination blood sample for immunogenicity testing for which valid results were reported.

The Per Protocol (PP) Population includes all subjects in the mITT Population with the following exclusions:

- Data from all available visits for subjects found to be ineligible at baseline.
- Data from all visits after major protocol deviations, such as:
    - Receipt of an incorrect study vaccination
    - Second or third vaccination not received
    - Second or third vaccination received out of window
- Receipt of any of the following:
    - Licensed, live vaccine within 30 days of any vaccination
    - Licensed, inactivated vaccine within 14 days of any vaccination
    - Investigational products at any time during study period

- Data from any visit that occurs substantially out of window

In the case of mis-randomization, subjects will be analyzed according to the study product actually received for all analysis populations.

9.4.2 Safety Data

Safety data will be summarized for the Safety Analysis Population. Subjects receiving a vaccination according to a study arm other than the study arm to which they were randomized, will be analyzed according to the vaccination(s) they actually received. Safety summaries will be presented for each dose group by presence or absence of ALFQ.

The proportion of subjects reporting at least one solicited AE will be summarized for each solicited AE, any systemic symptom, any local symptom, and any symptom. The 95% CI will be presented, and a Fisher's exact test will be performed to test for differences in the proportion of subjects reporting a solicited AE within dose groups between those with and without adjuvant.

Solicited AEs will be summarized by maximum severity for each day after each study vaccination for Days 1-8. The number, percentage (observed rate), and exact two-sided 95% CI for subjects reporting each solicited AE within 8 days following vaccination will be summarized. In addition, maximum severity for each solicited AE will be determined for each subject and reported by study arm and the resulting number and percentage of subjects will be summarized by severity grade (none, mild, moderate, severe). Summaries of solicited AEs will be presented separately by study arm for each study vaccination as well as overall study vaccinations.

Vaccine-related unsolicited AEs will be coded by MedDRA® for preferred term and system organ class (SOC). The number of SAEs, MAAEs, NOCMCs, and PIMMCs are likely to be small in this trial and will be reported by detailed listings showing the event description, MedDRA® preferred term and SOC, relevant dates (study vaccinations and AE duration), severity, relatedness, and outcome. If the number of events permits, a Fisher's exact test may be used to test for differences in unsolicited AE rates between adjuvant and non-adjuvant groups within dose levels, in a similar manner as for solicited AEs.

9.4.3 Immunogenicity Data

Immunogenicity data summaries and analysis will be presented for the mITT and PP populations. Descriptive statistics will be presented for each assay summarizing the geometric mean titer and its corresponding 95% CI, as well as the minimum and maximum at each time point.

The proportion of subjects within each dose level (with and without adjuvant) who develop at least a 4-fold rise from baseline in *C. jejuni* capsule-specific serum IgG antibodies will be summarized along with 95% CIs at Days 8, 29, 36, 57, 64, 85 and 113. The peak fold rise from baseline in *C. jejuni* capsule-specific serum IgG antibody titer across Days 8, 29, 36, 57, 64, 85 and 113 will be determined for each subject and summarized within each dose level (with and without adjuvant). Similarly, the maximum *C. jejuni* capsule-specific serum IgG antibody titer across all post-vaccination time points will be determined for each subject and summarized within each dose level (with and without adjuvant). Graphical presentations of immune responses may include reverse cumulative distribution (RCD) curves and longitudinal presentations of titers.

Exploratory immunogenicity endpoints will be summarized similarly.

9.4.4 Missing Values and Outliers

All attempts will be made to collect all data per protocol. As missing data are expected to be minimal, no imputation will be performed for missing values. Any data point that appears to be erroneous or inexplicable based on clinical judgment will be investigated as a possible outlier. If data points are identified as outliers, sensitivity analyses will be performed to examine the impact of including or excluding the outliers. Any substantive differences in these analyses will be reported.

10 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

The participating site will maintain appropriate medical and research records in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. The site will permit authorized representatives of the DMID, its designees, and appropriate regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance (QA) reviews, audits, and evaluation of the study safety and progress. These representatives will be permitted access to all source data and source documents, which include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

The study uses direct data entry (DDE) for the participating clinic site and the eCRFs serve as the source documents for data collected. Subjects will be trained to use a database to complete a web-based electronic memory Aid (e-Memory aid) and are expected to enter information in the e-memory aid each day of the solicited event collection period. Subjects using the e-memory aid will also be provided a paper memory aid for their use in the event they are unable to access the web-based system. If subjects need to use a paper memory aid, they will be asked to enter the information from the paper memory aid into the e-memory aid once they are able to access the web-based system. The e-Memory Aid is not considered source data. After clinic staff review and save the data, the data will be entered into Advantage eClinical as a source.

Subjects will record temperature, local and systemic symptoms and any new medications used following vaccination or changes to previously reported medications daily for 7 days after any vaccination.

Subjects will be instructed to contact the clinic staff immediately if they experience severe symptoms at any time during the study, for prompt follow-up in real time. The study clinic will be alerted in real time of any potential solicited events of Grade 3 severity entered in the e-memory aid. An email alert will be sent to the clinic site and the Emmes study team. Within one business day of site awareness, the site must attempt to follow up with the subject on the severe solicited event and send an email to Emmes confirming attempted follow up with the subject.

Instructions for completing the e-memory aid are provided in the MOP and in a separate e-memory aid instructions document that will be provided to the subjects at each vaccination. The site staff must review the e-memory aid information and interview the subject at the next scheduled visit. The subject-entered data will be available for review by the clinician during the clinical interview.

The site staff will be the data originators for the clinically reviewed data in Advantage eClinical® that will be used for the study endpoints. A list of all authorized site staff data originators will be included on the Study Personnel/Signature Responsibility List.

11 QUALITY CONTROL AND QUALITY ASSURANCE

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

The SDCC will implement QC procedures beginning with the data entry system and generate data QC checks that will be run on the database. Any missing data or data anomalies will be communicated to the participating site for clarification and resolution.

DMID-designated clinical monitors will verify that the clinical trial is conducted, and data are generated, documented (recorded), and reported in compliance with the protocol, ICH/GCP guidelines, and the applicable regulatory requirements. Clinical monitoring reports will be submitted to DMID.

12 DATA HANDLING AND RECORD KEEPING

12.1 Data Management Responsibilities

The site PI is responsible to ensure the accuracy, completeness, and timeliness of the data reported.

Data will be entered electronically over the Internet by site study staff into Advantage eClinical, developed and maintained by the SDCC. The eCRFs serve as the source documents for data collected. Paper CRFs derived from the eCRF are provided by the SDCC and are to be used only when Advantage eClinical is unavailable. Details on data handling procedures, procedures for data monitoring, and instructions for use of the system and completion of the eCRFs are provided in the study MOP, eCRF Instructions, and Advantage eClinical User's Guide. The sponsor and/or its designee will provide guidance to the site PI and other study personnel on making corrections to the eCRF.

12.2 Data Coordinating Center/Biostatistician Responsibilities

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

Data collection is the responsibility of the study personnel at the participating clinical study site under the supervision of the site PI. During the study, the site PI must maintain complete and accurate documentation for the study.

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

12.3 Data Capture Methods

Clinical (including, but not limited to, AE/SAEs, concomitant medications, medical history, physical assessments, and clinical laboratory values) and reactogenicity will be entered into eCRFs via a 21 CFR Part 11-compliant IDES provided by the study SDCC. The data system

includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

Site staff who are delegated the responsibility by the study PI will be the data originators for the clinical data entered directly into the eCRF. The central laboratory will be the data originator for the laboratory data reported by an automated reporting system. A list if all authorized data originators, including site staff, will be included on the Study Personnel/Signature Responsibility List.

12.4 Types of Data

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

12.5 Study Records Retention

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

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

13 CLINICAL MONITORING

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

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

14 PUBLICATION POLICY

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

Refer to:

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

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

As part of the result posting a copy of this protocol (and its amendments) and a copy of the SAP will be posted on ClincialTrials.gov.

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

The responsible party does not plan to request certification of delayed posting.

Refer to:

- Public Law 110-85, Section 801, Clinical Trial Databases
- 42CFR11
- NIH NOT-OD-16-149

15 LITERATURE REFERENCES

1. Fitzgerald, C., *Campylobacter.* Clin Lab Med, 2015. **35**(2): p. 289-98.
2. Same, R.G. and P.D. Tamma, *Campylobacter Infections in Children.* Pediatr Rev, 2018. **39**(11): p. 533-541.
3. Patrick, M.E., et al., *Features of illnesses caused by five species of Campylobacter, Foodborne Diseases Active Surveillance Network (FoodNet) - 2010-2015.* Epidemiol Infect, 2018. **146**(1): p. 1-10.
4. Jiang, Z.D. and H.L. DuPont, *Etiology of travellers' diarrhea.* J Travel Med, 2017. **24**(suppl_1): p. S13-s16.
5. Amour, C., et al., *Epidemiology and Impact of Campylobacter Infection in Children in 8 Low-Resource Settings: Results From the MAL-ED Study.* Clin Infect Dis, 2016. **63**(9): p. 1171-1179.
6. Kaakoush, N.O., et al., *Global Epidemiology of Campylobacter Infection.* Clin Microbiol Rev, 2015. **28**(3): p. 687-720.
7. Shakoor, S., A.K. Zaidi, and R. Hasan, *Tropical bacterial gastrointestinal infections.* Infect Dis Clin North Am, 2012. **26**(2): p. 437-53.
8. White, A.E., et al., *Characteristics of Campylobacter and Salmonella Infections and Acute Gastroenteritis in Older Adults in Australia, Canada, and the United States.* Clin Infect Dis, 2019. **69**(9): p. 1545-1552.
9. Kotloff, K.L., et al., *Burden and aetiology of diarrhoeal disease in infants and young children in developing countries (the Global Enteric Multicenter Study, GEMS): a prospective, case-control study.* Lancet, 2013. **382**(9888): p. 209-22.
10. Mullaney, S.B., et al., *Estimate of the annual burden of foodborne illness in nondeployed active duty US Army Service Members: five major pathogens, 2010-2015.* Epidemiol Infect, 2019. **147**: p. e161.
11. O'Brien, S.J., *The consequences of Campylobacter infection.* Curr Opin Gastroenterol, 2017. **33**(1): p. 14-20.
12. Jackson, B.R., et al., *Binational outbreak of Guillain-Barre syndrome associated with Campylobacter jejuni infection, Mexico and USA, 2011.* Epidemiol Infect, 2014. **142**(5): p. 1089-99.
13. Ajene, A.N., C.L. Fischer Walker, and R.E. Black, *Enteric pathogens and reactive arthritis: a systematic review of Campylobacter, salmonella and Shigella-associated reactive arthritis.* J Health Popul Nutr, 2013. **31**(3): p. 299-307.
14. Zhang, M., et al., *Association study between an outbreak of Guillain-Barre syndrome in Jilin, China, and preceding Campylobacter jejuni infection.* Foodborne Pathog Dis, 2010. **7**(8): p. 913-9.

15. Wierzba, T.F., et al., *Campylobacter infection as a trigger for Guillain-Barre syndrome in Egypt.* PLoS One, 2008. **3**(11): p. e3674.
16. Schiaffino, F., et al., *Antibiotic Resistance of Campylobacter Species in a Pediatric Cohort Study.* Antimicrob Agents Chemother, 2019. **63**(2).
17. Geissler, A.L., et al., *Increasing Campylobacter Infections, Outbreaks, and Antimicrobial Resistance in the United States, 2004-2012.* Clin Infect Dis, 2017. **65**(10): p. 1624-1631.
18. Ge, B., et al., *Antimicrobial resistance in campylobacter: susceptibility testing methods and resistance trends.* J Microbiol Methods, 2013. **95**(1): p. 57-67.
19. Peterson, M.C., *Rheumatic manifestations of Campylobacter jejuni and C. fetus infections in adults.* Scand.J Rheumatol., 1994. **23**: p. 167-170.
20. Bremell, T., A. Bjelle, and A. Svedhem, *Rheumatic symptoms following an outbreak of campylobacter enteritis: a five year follow up.* Ann Rheum.Dis, 1991. **50**: p. 934-938.
21. Gumpel, J.M., C. Martin, and P. Sanderson, J., *Reactive arthritis associated with campylobacter enteritis.* Ann Rheum Dis, 1981. **40**: p. 64-65.
22. Leung, F.Y., G.O. Littlejohn, and C. Bombardier, *Reiter's syndrome after Campylobacter jejuni enteritis.* Arthritis Rheum., 1980. **23**: p. 948-950.
23. van de Putte, L.B., et al., *Reactive arthritis after Campylobacter jejuni enteritis.* J Rheumatol., 1980. **7**: p. 531-535.
24. Berden, J.H., H.L. Muytjens, and L.B. van de Putte, *Reactive arthritis associated with Campylobacter jejuni enteritis.* Br.Med J, 1979. **1**: p. 380-381.
25. Nachamkin, I., *Campylobacter Enteritis and the Guillain-Barre Syndrome.* Curr Infect Dis Rep, 2001. **3**(2): p. 116-122.
26. Rees, J.H., et al., *Epidemiological study of Guillain-Barre syndrome in south east England [see comments].* J.Neurol.Neurosurg.Psychiatry, 1998. **64**: p. 74-77.
27. Mishu, B. and M.J. Blaser, *Role of infection due to Campylobacter jejuni in the initiation of Guillain-Barr:e syndrome.* Clin Infect.Dis, 1993. **17**: p. 104-108.
28. Prendergast, M.M. and A.P. Moran, *Lipopolysaccharides in the development of the Guillain-Barre syndrome and Miller Fisher syndrome forms of acute inflammatory peripheral neuropathies.* J Endotoxin Res, 2000. **6**(5): p. 341-59.
29. Moran, A.P. and M.M. Prendergast, *Molecular mimicry in Campylobacter jejuni lipopolysaccharides and the development of Guillain-Barre syndrome.* J Infect Dis, 1998. **178**(5): p. 1549-51.
30. Aspinall, G.O., A.G. McDonald, and H. Pang, *Lipopolysaccharides of Campylobacter jejuni serotype O:19: structures of O antigen chains from the serostrain and two bacterial isolates from patients with the Guillain-Barre syndrome.* Biochemistry, 1994. **33**(1): p. 250-5.
31. Alving, C.R., et al., *Adjuvants for human vaccines.* Curr Opin Immunol, 2012. **24**(3): p. 310-5.

32. Cawlfield, A., et al., *Safety, toxicity and immunogenicity of a malaria vaccine based on the circumsporozoite protein (FMP013) with the adjuvant army liposome formulation containing QS21 (ALFQ).* Vaccine, 2019. **37**(29): p. 3793-3803.

Appendix A. Schedule of Events

Study Visit [o]	**00**	**01**	**02**	**03**	**04**	**05**	**06**	**07**	**08**	**09**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**U/S[n]**	**E/T**
Visit Type- Clinic	x	x		x		x		x		x		x		x	x			x	x
Visit Type, Clinic or Virtual			x		x		x		x		x		x						
Visit Type- Safety Communication [q]																x	x		
Study Day	-30 to -2	1	3	8	15	29	31	36	43	57	59	64	71	85	113	240	420		
Visit Window [n]			±1	+1	±2	+2	±1	+1	±2	+2	±1	+1	±2	±2	±4	±7	±7		
Informed Consent [a]	x																		
Vaccination		x				x				x									
Demographics	x																		
Medical History [b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			x	x
Concomitant Medication Review [c]	x	x	x	x	x	x	x	x	x	x	x	x	x	x				x	x
Adverse Event Assessment [d, e]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Counsel on avoidance of pregnancy [p]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x				
Physical Exam [f]	x	x		x		x		x		x		x		x	x			x	x
Vital signs (BP, HR, Temp) [g]	x	x		x		x		x		x		x		x	x			x	x
Height & Weight	x																	x	
Review Eligibility	x	x																	
Urine Pregnancy Test [h, i]	x	x				x				x				x	x			x	x
Urine Dipstick for protein	x																	x	
Urine Opiate Test	x																	x	
Anti-HIV-1/2, HBsAg, Anti-HCV	x																	x	
HLA-B27	x																		
Hematology & Chemistry [j]	x			x				x				x						x	x

Study Visit [o]	**00**	**01**	**02**	**03**	**04**	**05**	**06**	**07**	**08**	**09**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**U/S[n]**	**E/T**
Continued on the next page																			
Reactogenicity Assessment [k]		x				x				x								x	
E-Memory Aid [l]		x	x	x		x	x	x		x	x	x						x	
Study Vaccination Site Examination		x	x	x		x	x	x		x	x	x						x	
Serum (Serology)		x		x		x		x		x		x		x	x			x	x
Blood (PBMCs) for ALS		x		x				x				x						x	
Blood (PBMCs) for Secondary Research		x		x		x		x		x		x		x	x			x	x
Serum for Secondary Research		x		x		x		x		x		x		x	x			x	x
Stool for Secondary Research [m]		x		x				x				x						x	x
Approx. blood mL by day	37	100		70		40		70		40		70		40	40			40	40

a) Prior to study procedures.
b) Complete medical history will be obtained by interview of subjects at the screening visit and will be updated on Day 1 prior to the first study vaccination. Interim medical history will be obtained by interview of subjects at follow-up visits after the first study vaccination. Contraception history will be collected for females of childbearing potential.
c) All current medications and medications taken within 30 days prior to signing the ICF. Concomitant medications taken within 30 days of enrollment through 28 days post last vaccination are collected in Advantage eClinical®.
d) AEs will be assessed through 28 days post last vaccination. SAEs will be followed throughout the study duration
e) Unsolicited AEs including MAAEs, NOCMCs, PIMMCs, and SAEs will be collected from subjects throughout their period of study participation and SAE to include concomitant medication(s) taken for these events.
f) An abbreviated physical examination will be performed at screening. A targeted physical examination may be performed at subsequent visits, if indicated based on review of medical history and any updates obtained by interview of subjects.
g) Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature.
h) Prior to vaccination.

i) A urine pregnancy test will be performed within 24 hours prior to study vaccinations and results must be negative and known prior to each study vaccination.
j) Hematology and Chemistry tests include WBC, Hgb, platelet count, ANC, sodium, potassium, creatinine, T. bili, ALT.
k) Reactogenicity assessments will occur prior to and ≥ 30 minutes post vaccination.
l) E-memory aid tools and education will be provided on the days of vaccination. E-memory aid review will occur 48 hours and 7 days post vaccination.
m) Stool kits will be provided during the visits preceding expected stool collection days.
n) Unscheduled study (U/S) events and Early Termination (E/T) events to occur as indicated.
o) Visit Window to be initiated at Day 1 of each vaccination day.
p) Counseling on avoidance of pregnancy will be performed on females of childbearing potential.
q) Safety Communication follow up visits may occur via phone or email communication.

Appendix B. Toxicity Table

Adverse Grading Event Grading Scale

This protocol is CDISC compliant. The modified Toxicity Grading Scale for Laboratory Abnormalities below serves as a guideline and are dependent upon institutional normal parameters.

Laboratory	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Sodium, low, mEq/L	132 – 135	130 – 131	<130
Sodium, high, mEq/L	146 – 147	148 – 149	150 or greater
Potassium, high, mEq/L	5.2 – 5.3	5.4 – 5.5	>5.5
Potassium, low, mEq/L	3.3 – 3.4	3.1 – 3.2	<3.1
Creatinine, high mg/dL (female)	1.0 - 1.1	1.2 - 2.0	>2
Creatinine, high mg/dL (male)	1.2 – 1.3	1.4 – 2.0	>2
Liver Function Tests (ALT) increase by factor	>1.0-2.5 x ULN	>2.5-5.0 x ULN	>5.0x ULN
Total bilirubin	>1.0-1.5 x ULN	>1.5-2.0 x ULN	>2.0 x ULN
Hgb (female), low g/dL	10.9-11.6	9.4 – 10.8	≤9.3
Hgb (male), low g/dL	13.1-13.2	12.5-13.0	≤12.4
WBC, increase, cells, x 10^3u/L	>11.1 –≤15.0	>15 - ≤ 20	>20.0
WBC, decrease, cells, x 10^3u/L	2.5-<4.4	1.5-<2.5	<1.5
ANC, x 10^3u/L	1.2-<1.7	0.9-<1.2	<0.9
Platelets, decrease, cells/mm^3	124,000-<134,000	100,000<124,000	<100,000
Urine protein	Trace	1+	2+

*** “ULN” is the upper limit of the normal range

Appendix C. PIMMCs list

Gastrointestinal disorders

- Celiac disease
- Crohn's disease
- Ulcerative colitis
- Ulcerative proctitis

Liver disorders

- Autoimmune cholangitis
- Autoimmune hepatitis
- Primary biliary cirrhosis
- Primary sclerosing cholangitis

Metabolic diseases

- Addison's disease
- Autoimmune thyroiditis (including Hashimoto thyroiditis)
- Diabetes mellitus type I
- Grave's or Basedow's disease

Musculoskeletal disorders

- Antisynthetase syndrome
- Dermatomyositis
- Juvenile chronic arthritis (including Still's disease)
- Mixed connective tissue disorder
- Polymyalgia rheumatic
- Polymyositis
- Psoriatic arthropathy
- Relapsing polychondritis
- Rheumatoid arthritis
- Scleroderma, including diffuse systemic form and CREST syndrome
- Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis
- Systemic lupus erythematosus
- Systemic sclerosis

Neuroinflammatory disorders

- Acute disseminated encephalomyelitis, including site-specific variants (e.g., non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculomyelitis)
- Cranial nerve disorders, including paralyses/paresis (e.g., Bell's palsy)
- Guillain-Barré syndrome, including Miller Fisher syndrome and other variants
- Immune-mediated peripheral neuropathies and plexopathies, including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy
- Multiple sclerosis
- Narcolepsy
- Optic neuritis
- Transverse myelitis
- Myasthenia gravis, including Eaton-Lambert syndrome

Skin disorders

- Alopecia areata
- Autoimmune bullous skin diseases, including pemphigus, pemphigoid, and dermatitis herpetiformis
- Cutaneous lupus erythematosus
- Erythema nodosum
- Morphoea
- Lichen planus
- Psoriasis
- Sweet's syndrome
- Vitiligo

Vasculitides

- Large vessels vasculitis including giant cell arteritis such as Takayasu's arteritis and temporal arteritis
- Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg-Strauss syndrome (allergic granulomatous angiitis), Buerger's disease thromboangiitis obliterans, necrotizing vasculitis and anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis

Others

- Antiphospholipid syndrome

- Autoimmune hemolytic anemia
- Autoimmune glomerulonephritis (including Immunoglobulin A (IgA) nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis)
- Autoimmune myocarditis/cardiomyopathy
- Autoimmune parotitis
- Autoimmune thrombocytopenia
- Good pasture syndrome
- Idiopathic pulmonary fibrosis
- Pernicious anemia
- Raynaud's phenomenon
- Sarcoidosis
- Sjögren's syndrome
- Stevens-Johnson syndrome
- Uveitis