A Phase II Study in Healthy Adults 18-64 Years Old to Assess the Safety, Reactogenicity and Immunogenicity of a Seqirus A/H7N9 Inactivated Influenza Vaccine Administered Intramuscularly With or Without MF59® Adjuvant

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Seqirus Inc.

IND Sponsor: DMID, NIAID

Lead Principal Investigator: Sharon E. Frey, MD

DMID Clinical Project Manager: Robin M. Mason, MS

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STATEMENT OF ASSURANCE

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

STATEMENT OF COMPLIANCE

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

- United States Code of Federal Regulations (CFR) 45 CFR Part 46: Protection of Human Subjects
- Food and Drug Administration (FDA) Regulations, as applicable: 21 CFR Part 50 (Protection of Human Subjects), 21 CFR Part 54 (Financial Disclosure by Clinical Investigators), 21 CFR Part 56 (Institutional Review Boards), 21 CFR Part 312 (Investigational New Drug Application), 21 CFR 812 (Investigational Device Exemptions)
- The International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use" (ICH) E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) Guidance for Industry," published in the Federal Register (83 Federal Register 8882 (2018)), including the latest finalized revision
- 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 assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH E6 Good Clinical Practice (GCP) guidelines.

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

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

Site Investigator Signature:

Signed: _____ Date: _____

Name
Title

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A/H1N1	Influenza A Virus of the H1N1 Subtype
A/H2N2	Influenza A Virus of the H2N2 Subtype
A/H3N2	Influenza A Virus of the H3N2 Subtype
A/H3N2v	Influenza A Virus of the H3N2 Variant Subtype
A/H5N1	Influenza A Virus of the H5N1 Subtype
A/H5N2	Influenza A Virus of the H5N2 Subtype
A/H5N6	Influenza A Virus of the H5N6 Subtype
A/H5N3	Influenza A Virus of the H5N3 Subtype
A/H5N8	Influenza A Virus of the H5N8 Subtype
A/H7N1	Influenza A Virus of the H7N1 Subtype
A/H7N7	Influenza A Virus of the H7N7 Subtype
A/H7N9	Influenza A Virus of the H7N9 Subtype
A/H9N2	Influenza A Virus of the H9N2 Subtype
AS03	Adjuvant System 03
AdvantageEDC^{SM}	Electronic Data Capture System
AE	Adverse Event/Adverse Experience
ALT	Alanine Aminotransferase
AESIs	Adverse Events of Special Interest
ANCA	Anti-Neutrophil Cytoplasmic Antibody
BARDA	Biomedical Advanced Research and Development Authority
BMI	Body Mass Index
BP	Blood Pressure
BPM	Beats Per Minute
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	Confidence Interval
CICP	Countermeasure Injury Compensation Program
CMS	Clinical Materials Services
CoA	Certificate of Analysis
CROMS	Clinical Research Operations and Management Support
Cr	Creatinine
CSL	Commonwealth Serum Laboratories
CSR	Clinical Study Report
CTAB	Cetyltrimethylammonium bromide
°C	Degrees Celsius
°F	Degrees Fahrenheit
D	Day(s)

DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FWA	Federal Wide Assurance
g/dL	Grams per Deciliter
GBS	Guillain-Barré Syndrome
GCP	Good Clinical Practice
GMT	Geometric Mean Titer
GSK	GlaxoSmithKline Biologicals
HA	Hemagglutinin
HAI	Hemagglutination Inhibition
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
HPAI	Highly Pathogenic Avian Influenza
HRSA	Health Resources and Services Administration
IATA	International Air Transport Association
IB	Investigator's Brochure
ICD	International Classification of Diseases
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IgG	Immunoglobulin G
IIV	Inactivated Influenza Virus Vaccine
IIV3	Trivalent Inactivated Influenza Vaccine
IIV4	Quadrivalent Inactivated Influenza Vaccine
IM	Intramuscular
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
IU/L	International Unit(s) per Liter
mcg	Microgram(s)
µL	Microliter(s)
MAAEs	Medically-Attended Adverse Events
MedDRA®	Medical Dictionary for Regulatory Activities
MF59®	MF59C.1 Adjuvant
mg/dL	Milligram(s) per Deciliter
mITT	Modified Intent-to-Treat

mL	Milliliter(s)
mmHg	Millimeters of Mercury
MOP	Manual of Procedures
N	Number of Subjects
NA	Neuraminidase
Neut	Neutralizing or Neutralization
NI	Neuraminidase Inhibiting
NIAID	National Institute of Allergy and Infectious Diseases, NIH, DHHS
NIH	National Institutes of Health
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
NOCMCs	New-Onset Chronic Medical Conditions
NVD	Novartis Vaccines and Diagnostics
OER	Office of Extramural Research
OHRP	Office for Human Research Protections
OTC	Over the Counter
PBS	Phosphate Buffered Saline
PHI	Personal Health Information
PIMMCs	Potentially Immune-Mediated Medical Conditions
PLT	Platelets
PP	Per Protocol
PREP Act	Public Readiness and Emergency Preparedness Act
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SOC	System Organ Class
SOP	Standard Operating Procedure
T. Bili	Total Bilirubin
US	United States
V	Visit(s)
VTEU	Vaccine and Treatment Evaluation Unit
WBC	White Blood Cells
WHO	World Health Organization

PROTOCOL SUMMARY

Title:

A Phase II Study in Healthy Adults 18-64 Years Old to Assess the Safety, Reactogenicity and Immunogenicity of a Seqirus A/H7N9 Inactivated Influenza Vaccine Administered Intramuscularly With or Without MF59® Adjuvant

Design of the Study:

This is a randomized, double-blinded, Phase II study in healthy males and non-pregnant females, 18-64 years of age. This clinical trial is designed to assess the safety, reactogenicity, and immunogenicity of a pre-pandemic 2017 monovalent inactivated influenza A/H7N9 virus vaccine (2017 H7N9 IIV) manufactured by Seqirus Inc (Seqirus) administered at different dosages (3.75 microgram [mcg], 7.5 mcg and 15 mcg of hemagglutinin (HA) per dose) given with MF59® adjuvant manufactured by Seqirus Inc. (Seqirus), or without adjuvant (15 mcg of HA per dose). Phosphate buffered saline (PBS) diluent manufactured by Patheon Manufacturing Services LLC will be used to achieve certain targeted doses. The 2017 H7N9 inactivated influenza vaccine (IIV) was manufactured using a reverse genetics-derived reassortant candidate vaccine virus IDCDC RG56B (H7N9), containing the HA and neuraminidase (NA) from low pathogenic influenza A/Hong Kong/125/2017 (H7N9) and the PB2, PB1, PA, NP, M and NS from A/Puerto Rico/8/1934 (H1N1).

Subjects who are in good health and meet all eligibility criteria (including a negative serum or urine pregnancy test for women of childbearing potential, history and physical exam) within 28 days prior to the first vaccination or on the day of, but prior to, first vaccination, will be randomized into one of 4 study groups as shown in Table 1. Baseline blood samples for clinical safety laboratories will be drawn prior to the first vaccine dose and will not be used to screen subjects for eligibility.

Reactogenicity will be measured by the occurrence of solicited injection site and systemic reactions from the time of each study vaccination through 7 days after each study vaccination. Unsolicited non-serious adverse events (AEs) will be collected from the time of each study vaccination through approximately 21 days after each study vaccination. Serious adverse events (SAEs),

medically-attended adverse events (MAAEs), including new-onset chronic medical conditions (NOCMCs), and potentially immune-mediated medical conditions (PIMMCs), will be collected from the time of the first study vaccination through approximately 12 months after the last study vaccination. Clinical laboratory evaluations for safety will be performed on venous blood collected prior to each study vaccination and approximately 7 days after each study vaccination.

Immunogenicity testing will include performing hemagglutinin inhibition (HAI) and neutralizing (Neut) antibody assays against the 2017 H7N9 vaccine virus on serum samples obtained immediately prior to each study vaccination (Days 1 and approximately Day 22), approximately 7 days after each study vaccination (Days 8 and 29), and approximately 21 and 180 days after the second study vaccination (Days 43 and 202).

Novel methods for identifying and assessing alternative correlates of protection against influenza infection are needed. We will assess the NA-specific antibody response to vaccination. In addition, we plan to determine the NA content of IIV using assays that are currently under development. If successful, we will determine whether the NA content correlates with the N9 NA-specific antibody response in a dosage-specific manner. If NA content of the vaccine is not determined, then we will determine whether the NA-specific antibody response increases with increasing dosage of vaccine based on the HA content.

Subjects who have not received the current season's licensed seasonal trivalent or quadrivalent influenza vaccine prior to enrollment may receive it anytime following completion of the Day 43 study visit or upon early termination.

Study Phase: II

Study Population: Approximately 371 individuals 18-64 years old, who have no history of influenza A/H7N9 infection or prior receipt of an influenza virus H7 subtype vaccine.

Number of Sites: Up to 7 Vaccine and Treatment Evaluation Unit (VTEU) sites

Description of Study Product or Intervention:

Two doses delivered intramuscularly (IM) approximately 21 days apart of a monovalent inactivated pre-pandemic influenza A/H7N9 vaccine (2017 H7N9 Inactivated Influenza Vaccine [IIV]) manufactured by Seqirus, at different dosages [3.75, 7.5 or 15 micrograms/0.5 milliliter (mL) of hemagglutinin (HA) from A/Hong Kong/125/2017 H7N9 vaccine per dose] administered with MF59® adjuvant (Seqirus) or without adjuvant [15 microgram (mcg) HA per dose].

Phosphate buffered saline (PBS) diluent manufactured by Patheon Manufacturing Services LLC is added to monovalent vaccine to achieve targeted HA content.

Study Objectives:

Primary:

Safety:

- To assess the safety and reactogenicity following receipt of two doses of 2017 H7N9 IIV administered IM at different dosages approximately 21 days apart given with or without MF59® adjuvant

Immunogenicity:

- To assess the serum HAI and Neut antibody responses approximately 21 days following receipt of two doses of 2017 H7N9 IIV administered IM at different dosages approximately 21 days apart with or without MF59® adjuvant.

Secondary:

Safety:

- To assess all unsolicited non-serious AEs following receipt of two doses of a 2017 H7N9 IIV administered IM at different dosages approximately 21 days apart with or without MF59® adjuvant
- To assess MAAEs including NOCMCs, PIMMCs, and all SAEs following receipt of two doses of a 2017 H7N9 IIV administered IM at different dosages approximately 21 days apart with or without MF59® adjuvant

Immunogenicity:

- To assess the serum HAI and Neut antibody responses approximately 7 and 21 days following receipt of a single dose, and approximately 7 days following receipt of two doses of 2017 H7N9 IIV administered IM at different dosages approximately 21 days apart with or without MF59® adjuvant.

Exploratory:

Immunogenicity:

- To assess the effects of age, sex, body mass index, and prior receipt of seasonal influenza vaccine(s) on serum HAI and Neut antibody responses following receipt of two doses of a 2017 H7N9 IIV administered IM at different dosages approximately 21 days apart with or without MF59® adjuvant.
- To assess, in at least a subset of samples, the cross-reactivity of serum HAI and Neut antibody responses to antigenically drifted variants of influenza A/H7 viruses following receipt of two doses of a 2017 H7N9 IIV administered IM at different dosages approximately 21 days apart with or without MF59® adjuvant.
- To assess the durability of serum HAI and Neut antibody responses at approximately 180 days following receipt of two doses of 2017 H7N9 IIV administered IM at different dosages approximately 21 days apart with or without MF59® adjuvant.
- To assess the NA content of the 2017 H7N9 IIV and determine the serum antibody responses to NA following receipt of 2017 H7N9 IIV.

Duration of Individual Subject Participation:	Approximately thirteen (13) months

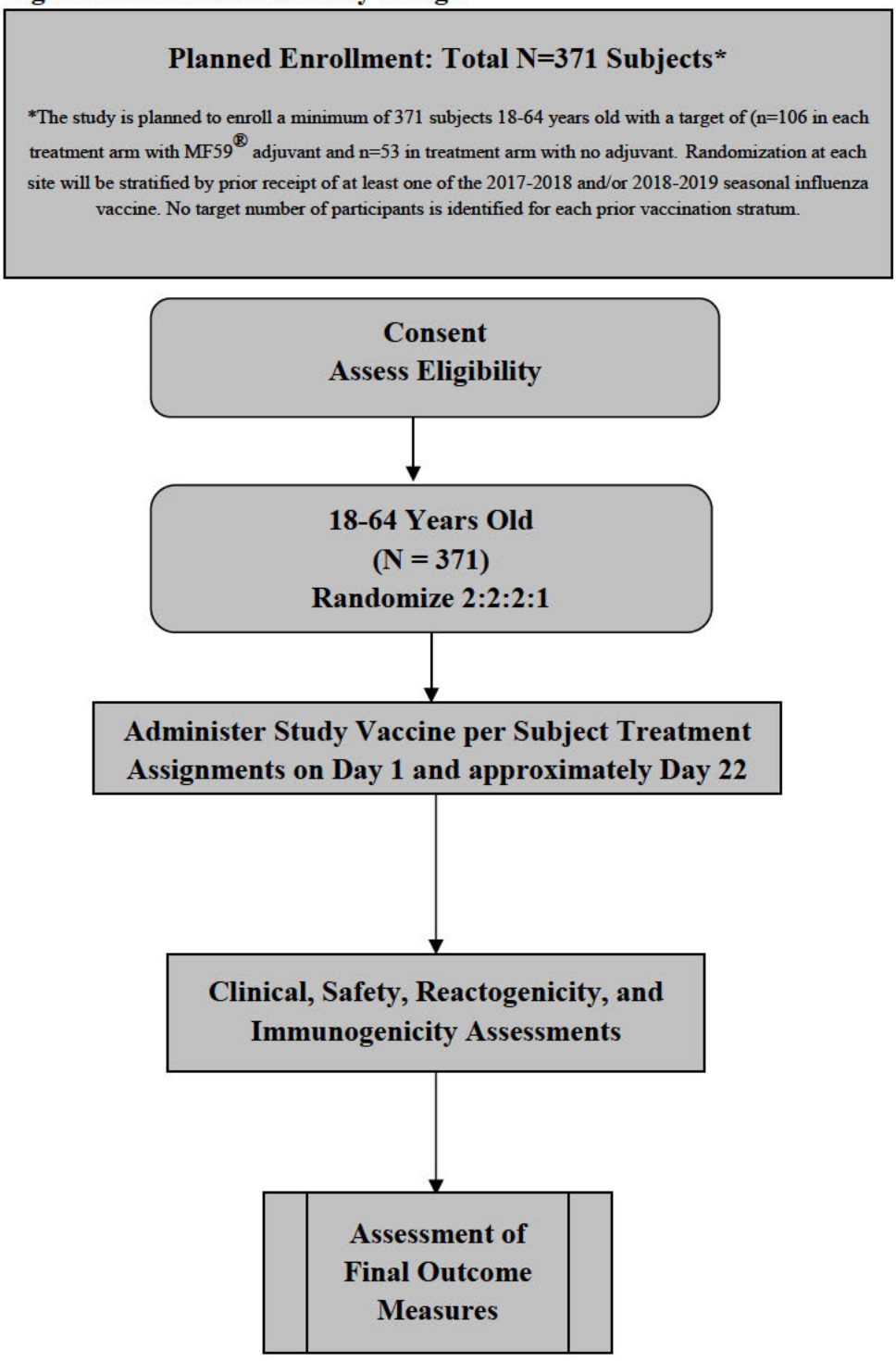
Estimated Time to Last Subject/Last Study Day: Approximately seventeen (17) months

Table 1: Study Design

Treatment Arms[1]	Day 1	Day 22
Group 1, n=106	Seqirus H7N9 vaccine 3.75 mcg plus MF59® adjuvant	Seqirus H7N9 vaccine 3.75 mcg plus MF59® adjuvant
Group 2, n=106	Seqirus H7N9 vaccine 7.5 mcg plus MF59® adjuvant	Seqirus H7N9 vaccine 7.5 mcg plus MF59® adjuvant
Group 3, n=106	Seqirus H7N9 vaccine 15 mcg plus MF59® adjuvant	Seqirus H7N9 vaccine 15 mcg plus MF59® adjuvant
Group 4, n=53	Seqirus H7N9 vaccine 15 mcg unadjuvanted	Seqirus H7N9 vaccine 15 mcg unadjuvanted

[1] Randomization will be stratified by site and prior receipt of at least one of the 2017-2018 and/or 2018-2019 seasonal influenza vaccine. No target number of participants is identified for each prior vaccination stratum.

Figure 1: Schematic of Study Design



1 KEY ROLES

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Data Coordinating Center:	The Emmes Company, LLC

2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background

The continued emergence of novel influenza A viruses in humans including subtypes H5N1, H3N2v, H7N7, H9N2, 2009 H1N1, and most recently H5N6 and H7N9, underscores the need for focused efforts to prepare for the next influenza pandemic [1-6]. Four pandemics occurred during the last century. It was estimated that during the 1918 influenza A/H1N1 pandemic as many as 40 million deaths occurred worldwide [7]. Excess mortality, high morbidity, and social disruption were all noted during the 1957 influenza A/H2N2 and the 1968 influenza A/H3N2 pandemics [8]. In April 2009, a novel influenza virus (2009 A/H1N1) originated in pigs and spread to humans around the world becoming the first pandemic of this century. In each of these influenza pandemics, human populations lacked significant levels of pre-existing immunity to a highly transmissible form of the virus enabling it to spread rapidly. Thus, each emergence of a new strain of influenza virus in the human population has the potential to result in a global public health emergency.

A major cornerstone of pandemic preparedness is the capacity to rapidly produce and deliver sufficient quantities of safe and effective strain-specific pandemic influenza vaccines. The threat of pandemic influenza in 1976 (swine influenza) and again in 1977 (Russian influenza) resulted in IIV development programs that provided important insights into variables influencing the immune responses to immunization [9, 10]. Vaccine- associated factors potentially affecting the immunogenicity of IIVs that were noted during the 1976 experience and have been refined in subsequent years include the amount of viral hemagglutinin (HA) protein in the vaccine, the number and intervals of doses administered, the addition of immune stimulating components (i.e., adjuvants), and the manufacturing methods used to produce the vaccine (i.e., whole virus, split virus, or purified surface antigen). Host-specific factors, including the recipient's age, their prior influenza infections and/or vaccinations, and the presence of underlying diseases and their treatments, all can influence the immune responses elicited by an influenza vaccine.

Serum antibodies targeting the influenza virus HA and NA, the major surface glycoproteins on influenza viruses, play a key role in protective immunity to influenza virus infection [11]. Since protection against infection with seasonal influenza virus strains has been shown to correlate with both serum HAI and Neut antibody levels, their measurements are used routinely to assess the immunogenicity of both seasonal and pandemic IIVs. Recent data also support an important role for neuraminidase inhibiting (NI) antibodies in protection against disease [12]. In a recent human influenza challenge study, serum NI antibody levels were also identified as an independent correlate of protection against influenza illness [13]. In the current study, we plan

to assess the NA content of 2017 H7N9 IIV and determine the correlation of NA content at different vaccine dosages with the elicited humoral antibody responses to the NA.

Several approaches have been used to increase the immunogenicity of IIVs. Standard-dose seasonal IIVs contain 7.5 mcg or 15 mcg of HA antigen per vaccine strain (for children aged <36 months) or 15 mcg of HA antigen per vaccine strain (for persons aged ≥36 months). Clinical studies evaluating increased HA-containing influenza vaccines performed over the past 35 years have shown dose-related increases in serum and mucosal antibody responses [14-22]. Higher HA dosage vaccines can lead to enhanced antibody responses in the elderly [23]. In 2009, a high-dose IIV containing 4 times the standard HA antigen per seasonal vaccine strain was approved in the United States (US) for use in individuals 65 years of age and older.

In general, clinical studies evaluating vaccines made from novel avian influenza viruses (e.g., A/H5N1, A/H7N7) suggest that these vaccines are substantially less immunogenic than those from other novel subtypes (e.g., 2009 A/H1N1 pandemic virus, even when administered at high HA dosages [24, 25]). Due to the poor immunogenicity of H5 and H7 vaccines, the inclusion of adjuvants was evaluated to assess their ability to boost anti-viral serum immunoglobulin G (IgG) levels. In the United States, aluminum salts are licensed as adjuvants in combination with several vaccines; however, their use in subvirion influenza A/H5N1 vaccines has shown either no effect or a very modest enhancement of immune responses compared to non-aluminum salt containing formulations [26-28]. In contrast, the use of oil-in-water emulsion adjuvants, most notably proprietary adjuvants AS03 and MF59® produced by GlaxoSmithKline Biologicals (GSK) and Seqirus, respectively, has resulted in increased antibody responses to IIVs containing novel HAs in numerous clinical trials [29-32].

Since 1997, MF59®, an oil-in-water adjuvant used in the seasonal influenza vaccine (FLUAD®) has been licensed for use in elderly individuals 65 years of age and older in 32 countries. Since then, FLUAD® has been licensed for children in several countries including South Africa (12 years of age and older), Mexico (6 to 36 months of age) and Canada (6 to less than 24 months). FLUAD® has been licensed in the US (65 years of age and older) since November 2015 (see Section 2.3.1). Clinical trials performed to assess the safety, immunogenicity and efficacy of novel HA-containing IIV formulations with and without MF59® reported that antibody GMTs and seroconversion rates were significantly higher among recipients of the adjuvanted vaccine compared to recipients of non-adjuvanted formulations [33-34].

Because of the substantial increases in antibody responses when these oil-in-water emulsion adjuvants were added to otherwise poorly immunogenic, novel HA influenza vaccines, they may be a critical component of the public health response to the next influenza pandemic. As part of its pandemic preparedness efforts, the US Government maintains stockpiles of unique HA-containing influenza vaccines, including those against influenza A/H7N9 and A/H5N1 viruses,

as well as MF59® adjuvants. The National Institute of Allergy and Infectious Diseases (NIAID) has conducted several clinical trials to evaluate avian influenza (A/H9N2, A/H7N9 and A/H5N1) vaccines administered with and without these adjuvants in healthy adult and elderly populations and found that the vaccines co-administered with adjuvants were well tolerated, exhibited dose-sparing and substantially increased the immunogenicity of strain-specific novel HA vaccines compared to non-adjuvanted formulations [35-41]. In response to emerging H5N8 viruses that have caused extensive outbreaks in domestic poultry and wild birds in South East Asia [42, 43], NIAID has recently completed enrollment for two clinical trials with an H5N8 vaccine produced by bioCSL Seqirus administered with either AS03 (GSK) or MF59® (Seqirus) in healthy individuals 19-64 years of age, (NCT02624219 and NCT03014310).

Since March of 2013 [43], avian influenza A/H7N9 viruses have continued to circulate in China causing discrete outbreaks (or waves) in humans with high mortality over the past 5 years. By late 2016, a "fifth wave" of outbreaks was identified in China and as of March 2018 a total of 1,567 laboratory-confirmed human infections with avian influenza A/H7N9 virus have been reported by the World Health Organization [44, 45]. Whereas most cases have been centered in and around mainland China, there have been several travel-associated cases, including two in travelers reported by Canada who were returning from China in early 2015 [46]. Most of the reported human cases have been associated with exposure to infected live poultry or contaminated environments, including markets where live poultry are sold. Influenza A/H7N9 viruses continue to be detected in poultry and their environments in the areas where human cases are occurring. Information to date indicates that these viruses do not transmit easily from human to human, with most isolates appearing to have retained their susceptibility to NA inhibitors [45]. Laboratory studies have shown that A/H7N9 influenza viruses readily infect cells from human respiratory tract tissue samples and can spread from ferret to ferret by droplet transmission, thereby increasing the concern about the pandemic potential of these viruses [47, 48].

Since the onset of the "fifth wave" of H7N9 outbreaks in October 2016, more human cases of H7N9 infection have been reported in China than any prior H7N9 epidemic wave [45]. In addition, an antigenically distinct lineage of these fifth wave H7N9 viruses known as the Yangtze River Delta lineage, has recently emerged and has been associated with an increasing number of human cases. This lineage has also resulted in a broader geographic spread of infected birds and human cases within China than previously seen. Further, several H7N9 viruses in the Yangtze River Delta lineage have recently acquired genetic changes characteristic of highly pathogenic avian influenza (HPAI) viruses and have now shown an increased ability to infect and kill poultry [44, 49].

The U.S. Department of Health and Human Services (DHHS) recently assessed H7N9 influenza virus as having a significant potential to cause a pandemic, and the greatest risk of causing severe disease. As a result, HHS has supported the production of fifth wave inactivated influenza

H7N9 vaccines for the U.S. stockpile and for an assessment of its safety and immunogenicity in clinical trials.

2.1.1 Public Readiness and Emergency Preparedness Act

For this protocol, the study products monovalent inactivated influenza 2017 H7N9 virus vaccine manufactured by Seqirus and adjuvant (MF59®) manufactured by Seqirus are covered under the Public Readiness and Emergency Preparedness Act (PREP Act). Under the PREP Act, covered persons are immune from liability actions brought from the administration or use of a covered countermeasure that is the subject of a declaration. The PREP Act provides immunity for covered persons (such as manufacturers, distributers, program planners, and other qualified persons who prescribe, administer, or dispense the 2017 H7N9 IIV with or without adjuvant) from tort liability, unless the injury was caused by willful misconduct.

The PREP Act also established the Countermeasures Injury Compensation Program (CICP) to provide compensation for serious injuries that occur as the result of the administration or use of certain countermeasures. Any requests for compensation must be filed within one year of administration or use of the countermeasure. Requests would go to the Health Resources and Services Administration (HRSA) Preparedness Countermeasures Injury Compensation Program (http://www.hrsa.gov/cicp/). Compensation may then be available for medical benefits, lost wages, and death benefits to eligible individuals for specified injuries in accordance with regulations published by the Secretary of HRSA. Eligibility for compensation and the injuries for which compensation may be available are further defined by regulation.

An individual who suffers a serious physical injury or death from administration and use of the 2017 H7N9 IIV with or without adjuvant may request benefits from the CICP. A serious physical injury means an injury that is life threatening, results in, or requires, medical or surgical intervention to prevent permanent impairment of a body function, or permanent damage to body structure. The CICP is the payer of last resort. This means that it only covers expenses or provides benefits that other third-party payers, such as health insurance, the Department of Veterans Affairs, or Workers' Compensation programs don't have an obligation to pay.

If no funds have been appropriated to the compensation program, the Secretary of HRSA does not make a final determination on the individual's request within 240 days, or if the individual decides not to accept the compensation, the injured individual or his representative may pursue a tort claim in the US District Court for the District of Columbia, but only if the claim involves willful misconduct, is pled with particularity required under the PREP Act, verified, and accompanied by an affidavit by a physician who did not treat the individual and certified medical records. Any award is reduced by any public or private insurance or worker's compensation available to the injured individual. Awards for non-economic damages, such as pain, suffering,

physical impairment, mental anguish, and loss of consortium are also limited. If the individual accepts compensation, or if there is no willful misconduct, then the individual does not have a tort claim that can be filed in a United States Federal or a State court.

2.2 Scientific Rationale

2.2.1 Purpose of Study

As part of the US Government's past pandemic preparedness efforts, Sanofi Pasteur under contract to the Biomedical Advanced Research and Development Authority (BARDA)/DHHS), produced several novel pre-pandemic vaccines that were evaluated by NIAID's VTEU sites to assess their safety, reactogenicity, and immunogenicity when mixed prior to administration with either AS03 or MF59® oil-in-water adjuvants manufactured by GSK and Seqirus, respectively. In general, these trials have demonstrated that adjuvant use results in a significant dose-sparing effect. NIAID has recently completed enrollment of two "mix and match" clinical trials using an H5N8 vaccine antigen produced by Seqirus and mixed with either AS03 or MF59® adjuvants (NCT03014310, NCT02624219).

The large number of human infections starting with the "fifth wave" of H7N9 outbreaks in late 2016 has raised the pandemic risk assessment of influenza A/H7N9 viruses circulating in China. The Yangtze River Delta lineage, a distinct H7N9 viral lineage, has now emerged and has been associated with many of the cases in the fifth epidemic wave. This has also resulted in a broader geographic spread of infected birds and human cases within China than previously reported. Further, several H7N9 viruses in the Yangtze River Delta lineage have recently acquired genetic changes characteristic of HPAI viruses and have now shown an increased ability to infect and kill poultry [45, 49]. To date, no cases of H7N9 from the new lineage have been identified in birds or people infected outside of China; however, a few cases have been identified in Hong Kong and Taiwan in infected travelers returning from China. Importantly, antigenic analysis of the fifth wave H7N9 viruses and serology studies indicate that the stockpiled H7N9 vaccine manufactured several years ago does not induce protective HAI or Neut antibodies against the Yangtze River Delta lineage. Hence, there is broad consensus across HHS and interagency leadership that a new vaccine should be developed that would be effective against the currently predominating H7N9 viruses.

Several candidate vaccine viruses are under evaluation by the Center for Disease Control (CDC) and the World Health Organization (WHO) H5 Reference Laboratories Network. Under contract to BARDA/DHHS, Seqirus has produced a monovalent inactivated influenza pre-pandemic 2017 A/H7N9 virus vaccine (2017 H7N9 IIV). The availability of the US Government-stockpiled MF59® (Seqirus) oil-in-water adjuvant provides an opportunity to determine if dose-sparing

effects occur when mixing the Seqirus 2017 H7N9 vaccine with the MF59® adjuvant (See Section 4.1 for additional details on the H7N9 vaccine).

The goal of this clinical trial is to assess the safety, reactogenicity and immunogenicity of two doses of the 2017 H7N9 IIV administered with or without MF59® in healthy adults. The 2017 H7N9 IIV manufactured by Seqirus will be administered IM at different dosages mixed at the site with MF59® [3.75, 7.5 and 15 mcg HA per dose) or given without MF59® (15 mcg HA per dose) to evaluate the dose-sparing potential of the adjuvant. Data from phase I clinical trials of avian IIVs suggest that they are poorly immunogenic and require multiple high-doses or the inclusion of an adjuvant to induce serum HAI titer of 40 or greater against the study vaccine virus. In previous NIAID- sponsored clinical trials of 2013 H7N9 IIV, 2 doses of non-adjuvanted 15 or 45 mcg of HA per dose did not confer significant seroprotection [37, 39]. In addition to assessing antigen-sparing strategies, another goal of this study is to assess, in at least a subset of samples, whether serum IgG elicited by the 2017 H7N9 IIV recognizes antigenically drifted variants of influenza A/H7 viruses. Since antibodies targeting the NA may represent an independent correlate of protection against influenza infection [11-13], we plan to assess the NA content of the 2017 H7N9 vaccine and determine if there is a dose-response relationship of NA content with elicited humoral antibody responses to the N9 NA [50].

Based on previously conducted studies with a 2013 H7N9 IIV manufactured by Sanofi administered with or without MF59®, we anticipate that two doses of the 2017 H7N9 IIV administered IM at different dosages with MF59® adjuvant approximately 21 days apart will be well-tolerated and more immunogenic compared to the non-adjuvanted vaccine in healthy adult individuals [37, 51].

2.2.2 Study Population

The study population will be representative of the general public from each of the VTEU participating sites. Children will not be included as this study is designed for healthy adult subjects between the ages of 18-64 years.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

The potential risks of participating in this trial are those associated with having blood drawn, the IM injection and possible reactions to the 2017 H7N9 IIV, with or without PBS diluent and/or MF59® adjuvant, and breach of confidentiality.

Drawing blood may cause transient discomfort and fainting. Fainting is usually transient and managed by having the subject lie down and elevate his/her legs. Bruising at the blood draw site may occur, but can be prevented or lessened by applying pressure to the blood draw site for a few minutes after the blood is taken. IM injection may also cause transient discomfort and fainting. Drawing blood and IM injection may cause infection. The use of aseptic (sterile) technique will make infection at the site where blood will be drawn or where the study vaccination will be given extremely unlikely.

There is a small risk to subjects who report that they are in good health but who have an unknown health problem at the time of vaccination. This trial will screen by physical exam, history, and vital signs. To minimize the risk, subjects will not receive the second study vaccination if the subject meets any of the exclusion criteria listed in Section 8.6.2.

There is potential for AEs to occur more frequently in the adjuvanted vaccine groups [32] than in the non-adjuvanted group and there is potentially a higher risk for AEs to occur more frequently in the higher dose influenza antigen groups than in the lower dose viral antigen groups. The 2017 H7N9 IIV to be used in this study has not been tested for safety in animals and has not previously been evaluated in humans. The DMID, NIAID has sponsored five Phase II clinical trials to assess the safety, reactogenicity, and immunogenicity of one or two IM doses of a monovalent A/H7N9 vaccine produced by Sanofi Pasteur, Swiftwater, PA, administered with or without AS03 or MF59® in healthy subjects (DMID Protocols: 13-0032, NCT01938742; 13-0033, NCT01942265; 13-0034, NCT02213354; 13-0044, NCT02586792; and 14-0015, NCT02921997). Overall, the study products administered in these clinical trials were generally safe and well-tolerated. For DMID Protocol 13-0032, nine SAEs were reported. All were assessed as being not related to study product. Two AEs of special interest (AESIs) were reported in this clinical trial: Hashimoto's disease (assessed as not related to study product) and Hashimoto's thyroiditis (assessed as related to study product). For DMID Protocol 13-0033, sixteen SAEs were reported, fifteen of these SAEs were assessed as being not related to study product. One SAE was considered to be related: acute inferior myocardial infarction. Two AESIs were reported in this clinical trial: psoriasiform dermatitis and celiac disease (both assessed as not related to study product because both disorders pre-existed to vaccination, but both disorders received the diagnosis after vaccination).

The manufacturing process used to produce the monovalent 2017 H7N9 IIV is the same as for the US licensed product Agriflu® seasonal influenza vaccine with the exception of the final steps being performed at the Parkville manufacturing site, which is an FDA-approved manufacturing site for Afluria®, but not Agriflu®. The current H7N9 monovalent subunit IIV to be used in this trial was derived from the influenza virus A/Hong Kong/125/2017 (H7N9). The potential risks to subjects are anticipated to be similar to those observed for Seqirus' unadjuvanted, licensed seasonal IIV, Agriflu® (see Agriflu® Package Insert).

Occasionally, adult recipients of unadjuvanted licensed, IIVs may develop influenza-like reactions, such as fever, feverishness, fatigue, malaise, myalgia, arthralgia, headache, and/or nausea. Some subjects may develop reactions at the injection site, including pruritus, and/or ecchymosis due to the vaccination procedure, erythema, induration/swelling, pain, and/or tenderness [53].

Acute and potentially life-threatening allergic reactions (i.e., anaphylaxis) are also possible. These reactions occur in about 1 in 4 million people given a licensed vaccine. These reactions can manifest as hives, angioedema, bronchospasm, tachycardia, or hypotension. If these reactions occur, they can usually be stopped by the administration of emergency medications by the study personnel. As with any vaccine or medication, there is a very small chance of a death, although researchers do not expect this to occur.

During the swine influenza (H1N1) vaccine campaign of 1976, some recipients developed a paralytic illness called GBS. GBS is an acute inflammatory neuropathy characterized by weakness, hyporeflexia or areflexia, and elevated protein concentrations in cerebrospinal fluid. The rate of GBS was significantly increased in individuals receiving the 1976 swine influenza (H1N1) vaccine at about 1 per 100,000 vaccine recipients. This syndrome has not been seen consistently with other influenza vaccines. Most persons who develop GBS recover completely, although the recovery period may be as little as a few weeks or as long as a few years. About 30% of those with GBS still have residual weakness after 3 years and about 3% may suffer a relapse of muscle weakness and tingling sensations many years after the initial attack. Intensive surveillance of GBS after administration of IIVs since 1976 has shown a slight increase in risk over background cases (more than one additional case of GBS per million persons) following vaccination, typically with onset within 6 weeks after vaccination [54]. Interestingly, although vaccination rates have increased in the last 10 years, the numbers of reported cases of vaccine-associated GBS have declined [55]. A recent study in Canada showed that the 2009 H1N1 vaccine was associated with a small but significant risk of GBS in persons 50 years and older [56]. An active, population-based surveillance study conducted in the United States during the

2009-2010 influenza season found less than 1 excess GBS case per million doses of 2009 H1N1 vaccine administered – a rate similar to that associated with some previously administered annual influenza vaccines [57-59]. Another study using the Medicare system showed an elevated risk of GBS with 2009 H1N1 vaccination (incidence rate ratio = 2.41, 95% confidence interval: 1.14, 5.11; attributable risk = 2.84 per million doses administered, 95% confidence interval: 0.21, 5.48) [60]. An international collaboration study also supported a conclusion of an association between 2009 H1N1 vaccination and GBS [61]. It is unknown if the administration of the 2017 H7N9 IIV to be used in this clinical trial will result in an increased incidence of GBS as the mechanism leading to this AE has not been completely elucidated.

Numerous studies have shown that the MF59® adjuvant significantly improved the immunogenicity of inactivated subunit influenza virus vaccines, with a clinically acceptable increase in the incidence of injection site reactions [33-35, 37, 39-41, 51, 62-64].There was, as expected, a general tendency for an increased risk of slightly more mild and transient solicited injection site (especially tenderness/pain) and systemic reactions in subjects exposed to MF59®, while there was a consistent indication for a similar or decreased overall risk of all unsolicited AEs, autoimmune diseases, new onset of chronic diseases, cardiovascular diseases, SAEs, hospitalizations, and deaths, when compared to non MF59®-adjuvanted influenza vaccines. Additional information can be found in the FDA-licensed FLUAD® package insert.

Subjects should be informed that they might experience the following injection site and systemic AEs after vaccination with MF59®-adjuvanted vaccines:

Injection site reactions: redness, swelling, pain, ecchymosis, induration.

Systemic reactions: fever, malaise, chills, fatigue, headache, sweating, myalgia, arthralgia, shivering.

Most reactions are mild or moderate and resolve spontaneously within one to two days.

The following adverse events have been spontaneously reported during post-approval use of FLUAD® in the United States since March 2017 (package insert). Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the vaccine.

Blood and lymphatic system disorders: Thrombocytopenia (some cases were severe with platelet counts less than 5,000 per mm3), lymphadenopathy
General disorders and administration site conditions: Extensive swelling of injected limb lasting more than one week, injection site cellulitis-like reactions (some cases of swelling, pain, and redness extending more than 10 cm and lasting more than 1 week)

Immune system disorders: Allergic reactions including anaphylactic shock, anaphylaxis and angioedema

Musculoskeletal and connective tissue disorders: Muscular weakness

Nervous system disorders: Encephalomyelitis, Guillain-Barré Syndrome, convulsions, neuritis, neuralgia, paraesthesia, syncope, presyncope

Skin and subcutaneous tissue disorders: Generalized skin reactions including erythema multiforme, urticaria, pruritis or non-specific rash

Vascular disorders: Vasculitis with transient renal involvement

There is substantial clinical experience with MF59® adjuvant. In a very extensive set of clinical studies, MF59® has proven to be an effective vaccine adjuvant with an acceptable safety and tolerability profile, resulting in the licensure of an MF59®-adjuvanted interpandemic seasonal subunit IIV3 (FLUAD®) in 32 countries worldwide including the US (US licensed since November 2015). FLUAD® was initially licensed for commercial sale in 1997 in Italy, and is currently approved with either a Mutual Recognition Procedure or a National Procedure in 11 EU countries. It is also currently registered for use in 19 other countries worldwide. This adjuvanted vaccine is currently licensed for immunization of elderly people 65 years of age and above (with the exceptions in South Africa, where FLUAD® is licensed in subjects 12 years of age and above, and in Canada where FLUAD® is licensed for use in both adults 65 years of age and older and children ≥6 to <24 months of age).

It is unknown if the Seqirus 2017 H7N9 IIV (A/Hong Kong/125/2017) with or without MF59® adjuvant poses any risks to an unborn child. Tsai et al. evaluating the clinical trial database of all Novartis vaccine studies from 1991-2009 found that the distribution of pregnancy outcomes (normal, abnormal, or ending in induced abortion) were similar in subjects exposed to MF59®-adjuvanted and non-adjuvanted influenza vaccines at any time in pregnancy [65]. In a comparative cohort study, Heikkinen et al. found no differences in gestational diabetes, preeclampsia, stillbirth, low birth weight, neonatal deaths, or congenital malformations among MF59-adjuvanted A/H1N1 vaccinated and unvaccinated cohorts [66].

Subjects will be asked to provide personal health information (PHI). All attempts will be made to keep this PHI confidential within the limits of the law. However, there is a chance that unauthorized persons will see the subject's PHI. All study records will be kept in a locked file cabinet or maintained in a locked room at the participating VTEU sites. Electronic files will be password-protected. Only people who are involved in the conduct, oversight, monitoring, or auditing of this trial will be allowed access to the PHI that is collected. Any publications from

this trial will not use information that will identify subjects by name. Organizations that may inspect and/or copy research records maintained at the participating VTEU sites for quality assurance and data analysis include groups such as the local Institutional Review Board (IRB), NIAID, and the FDA.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by US Law. This web site will not include information that can identify subjects.

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

2.3.2 Potential Benefits

Vaccination using the 2017 H7N9 IIV with or without MF59® adjuvant may or may not provide protection against a serious disease with the 2017 H7N9 IIV, should the participant be exposed. The duration of any such protection is currently unknown. The 2017 H7N9 IIV with or without MF59® adjuvant is not expected to offer protection against circulating seasonal influenza viruses. There may be pandemic preparedness benefits to society in the future if the vaccine and adjuvants being evaluated in this clinical trial prove to be sufficiently safe and immunogenic and can be employed if a need for widespread influenza 2017 H7N9 vaccination occurs.

3 STUDY DESIGN, OBJECTIVES AND ENDPOINTS OR OUTCOME MEASURES

3.1 Study Design Description

This is a randomized, double-blinded, Phase II study in 371 healthy males and non-pregnant females, 18-64 years of age. This clinical trial is designed to assess the safety, reactogenicity, and immunogenicity of a pre-pandemic 2017 H7N9 IIV manufactured by Seqirus administered at different dosages (3.75 mcg, 7.5 mcg and 15 mcg of HA per dose, n=106 per arm) given with MF59® adjuvant manufactured by Seqirus, or without adjuvant (15 mcg of HA per dose, n=53). The 2017 H7N9 IIV was manufactured using a reverse genetics-derived reassortant candidate vaccine virus IDCDC RG56B (H7N9), containing the HA and NA from low pathogenic influenza A/Hong Kong/125/2017 (H7N9) and the PB2, PB1, PA, NP, M and NS genes from A/Puerto Rico/8/1934 (H1N1). Phosphate buffered saline (PBS) diluent manufactured by Patheon Manufacturing Services LLC will be used to achieve certain targeted dosages.

Subjects who are in good health and meet all eligibility criteria (including a negative serum or urine pregnancy test for women of childbearing potential, history and physical exam) within 28 days prior to the first vaccination or on the day of, but prior to, first vaccination, will be randomized into one of 4 study groups as shown in Table 1. Baseline bloods samples for clinical safety laboratories will be drawn prior to the first vaccine dose and will not be used to screen subjects for eligibility.

Reactogenicity will be measured by the occurrence of solicited injection site and systemic reactions from the time of each study vaccination through 7 days after each study vaccination. Unsolicited non-serious AEs will be collected from the time of each study vaccination through approximately 21 days after each study vaccination. SAEs, MAAEs, including NOCMCs, and PIMMCs, will be collected from the time of the first study vaccination through approximately 12 months after the last study vaccination. Clinical laboratory evaluations for safety will be performed on venous blood collected prior to each study vaccination and approximately 7 days after each study vaccination.

Immunogenicity testing will include performing HAI and Neut antibody assays against the 2017 H7N9 vaccine virus on serum samples obtained immediately prior to each study vaccination (Days 1 and approximately Day 22), approximately 7 days after each study vaccination (Days 8 and 29), and approximately 21 and 180 days after the second study vaccination (Days 43 and 202).

Novel methods for identifying and assessing alternative correlates of protection against influenza infection are needed. We will assess the dose related response of NA-specific antibody to

vaccination. In addition, if an assay becomes available, we plan to determine the NA content of inactivated influenza vaccine. If possible, we will determine whether the NA content in a dosage-specific manner correlates with the N9 NA-specific antibody response. If NA content of the vaccine is not determined, then we will determine whether the NA-specific antibody response increases with increasing dosage of vaccine based on the HA content.

Subjects who have not received the current season's licensed seasonal IIV3 or IIV4 prior to being enrolled in the study may receive it anytime following completion of the Day 43 study visit or upon early termination.

For additional details on study procedures and evaluations and study schedule by study visits/days, see Sections 6 and 7 and APPENDIX A: SCHEDULE OF PROCEDURES AND EVALUATIONS.

3.2 Study Objectives

3.2.1 Primary

Safety:

- To assess the safety and reactogenicity following receipt of two doses of 2017 H7N9 IIV administered IM at different dosages approximately 21 days apart given with or without MF59® adjuvant

Immunogenicity:

- To assess the serum HAI and Neut antibody responses approximately 21 days following receipt of two doses of 2017 H7N9 IIV administered IM at different dosages approximately 21 days apart with or without MF59® adjuvant.

3.2.2 Secondary

Safety:

- To assess all unsolicited non-serious AEs following receipt of two doses of a 2017 H7N9 IIV administered IM at different dosages approximately 21 days apart with or without MF59® adjuvant

- To assess MAAEs including NOCMCs, PIMMCs, and all SAEs following receipt of two doses of a 2017 H7N9 IIV administered IM at different dosages approximately 21 days apart with or without MF59® adjuvant

Immunogenicity:

- To assess the serum HAI and Neut antibody responses approximately 7 and 21 days following receipt of a single dose, and approximately 7 days following receipt of two doses of 2017 H7N9 IIV administered IM at different dosages approximately 21 days apart with or without MF59® adjuvant.

3.2.3 Exploratory

Immunogenicity:

- To assess the effects of age, sex, body mass index, and prior receipt of seasonal influenza vaccine(s) on serum HAI and Neut antibody responses following receipt of two doses of a 2017 H7N9 IIV administered IM at different dosages approximately 21 days apart with or without MF59® adjuvant.

- To assess, in at least a subset of samples, the cross-reactivity of serum HAI and Neut antibody responses to antigenically drifted variants of influenza A/H7 viruses following receipt of two doses of a 2017 H7N9 IIV administered IM at different dosages approximately 21 days apart with or without MF59® adjuvant.

- To assess the durability of serum HAI and Neut antibody responses at approximately 180 days following receipt of two doses of 2017 H7N9 IIV administered IM at different dosages approximately 21 days apart with or without MF59® adjuvant.

- To assess the NA content of the 2017 H7N9 IIV and determine the serum antibody responses to NA following receipt of 2017 H7N9 IIV.

3.3 Study Endpoints or Outcome Measures

3.3.1 Primary

Safety:

- Occurrence of study vaccine-related SAEs from the time of the first study vaccination through approximately 12 months after the last study vaccination.

- Occurrence of solicited injection site and systemic reactogenicity events from the time of each study vaccination through 7 days after each study vaccination.

- Occurrence of clinical safety laboratory adverse events from the time of each study vaccination through approximately 7 days after each study vaccination.

Immunogenicity:

- For HAI and Neut antibodies, percentage of subjects achieving seroconversion against the influenza 2017 H7N9 study vaccine strain (defined as either a pre-vaccination titer <10 and a post-vaccination titer ≥40 or a pre-vaccination titer ≥10 and a minimum four-fold rise in post-vaccination titer) at approximately 21 days after the second study vaccination (Study Day 43).

- For HAI and Neut antibodies, percentage of subjects achieving titer ≥40 against the influenza 2017 H7N9 study vaccine strain at approximately 21 days after the second study vaccination (Study Day 43).

- GMTs of serum HAI and Neut antibodies against the influenza 2017 H7N9 vaccine strain at approximately 21 days after the second study vaccination (Study Day 43).

3.3.2 Secondary

Safety:

- Occurrence of study vaccine-related unsolicited non-serious AEs from the time of each study vaccination through approximately 21 days after each study vaccination.

- Occurrence of all unsolicited adverse events, regardless of the assessment of seriousness or relatedness, from the time of each study vaccination through approximately 21 days after each study vaccination.

- Occurrence of MAAEs, including NOCMCs, and PIMMCs from the time of the first study vaccination through approximately 12 months after the last study vaccination.

- Occurrence of all SAEs, regardless of the assessment of relatedness, from the time of the first study vaccination through approximately 12 months after the last study vaccination.

Immunogenicity:

- For HAI and Neut antibodies, percentage of subjects achieving seroconversion against the influenza 2017 H7N9 vaccine strain at approximately 7, 21, and 28 days after the first study vaccination (Study Day 8, 22, 29).

- For HAI and Neut antibodies, percentage of subjects achieving titers of 40 or greater against the influenza 2017 H7N9 vaccine strain at baseline and approximately 7, 21, and 28 days after the first study vaccination (Study Day 8, 22, 29).

- GMTs of serum HAI and Neut antibodies against the influenza 2017 H7N9 vaccine virus at baseline and approximately 7, 21, and 28 days after the first study vaccination (Study Day 8, 22, 29).

3.3.3 Exploratory

Immunogenicity:

- For HAI and Neut antibodies, percentage of subjects achieving seroconversion and the GMTs of serum HAI antibody against the 2017 H7N9 study vaccine strain approximately 21 and 180 days after the second study vaccination (Study Day 43 and 202), stratified by sex, body mass index, and prior receipt of seasonal influenza vaccine(s).

- For HAI and Neut antibodies, for at least a subset of subjects, percentage achieving seroconversion, percentage with titer ≥40, and GMTs against antigenically drifted variants of influenza A/H7 viruses at baseline and approximately 21 and 180 days after the second study vaccination (Study Day 43 and 202).

- For HAI and Neut antibodies, percentage of subjects achieving seroconversion, percentage with titer ≥40, and GMTs against the 2017 H7N9 study vaccine strain at approximately 180 days after the second study vaccination (Study Day 202).

Percentage of subjects with detectable levels of serum N9 NA-specific antibody elicited by 2017 H7N9 vaccination. Serum N9 NA-specific antibody responses elicited by H7N9 vaccination will be correlated with NA content (if NA content results are available) at baseline and approximately 7 and 21 days after the first study vaccination (Study Day 1, 8 and 22) and 7, 21 and 180 days after the second study vaccination (Study Day 29, 43 and 202). If the NA content of the vaccine is not determined, then we will determine whether the NA-specific antibody response increases with increasing dosage of vaccine based on the HA content.

4 STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

4.1 Study Product Description

2017 H7N9 IIV

Seqirus has developed an H7N9 monovalent inactivated, "subunit" influenza virus vaccine, 2017 H7N9 IIV manufactured from a reverse genetics-derived reassortant virus (A/Hong Kong/125/2017[H7N9]-PR8-IDCDC-RG56B) containing the HA and NA from influenza A/Hong Kong/125/2017 (H7N9) and the PB2, PB1, PA, NP, M and NS genes from A/Puerto Rico/8/1934 (H1N1). The manufacturing process for this monovalent 2017 H7N9 IIV is similar to the US-approved Agriflu seasonal influenza vaccine with the exception of the final steps being performed at the Parkville manufacturing site, which is an FDA-approved manufacturing site for Afluria®, but not Agriflu®. [redacted]

MF59® Adjuvant

[redacted]

PBS Diluent

The PBS diluent was manufactured by Patheon Manufacturing Services LLC in accordance with Good Manufacturing Practice Regulations.

4.1.1 Formulation, Storage, Packaging, and Labeling

2017 H7N9 IIV

The 2017 H7N9 IIV is provided as a clear, sterile, buffered aqueous solution containing primarily the outer membrane proteins, HA and NA and preservative in a 5 mL clear, Type 1

borosilicate glass, multi-dose vial. For the purposes of this protocol, each vial will be used as a single entry, single dose vial.

Each multi-dose vial contains thimerosal, a mercury derivative, added as a preservative. Each 0.5 mL dose of non-adjuvanted vaccine contains approximately 50 mcg of thimerosal. The vials containing study product must be stored at 2°C to 8°C (36°F to 46°F). Do not freeze. No component of this vaccine contains latex.

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Specific mixing instructions are included in the MOP to achieve specific dosages.

The 2017 H7N9 IIV doses administered with adjuvant will be admixed with MF59® resulting in administration of an adjuvanted 2017 H7N9 IIV.

PBS Diluent

[redacted] It is essentially clear and slightly opalescent in color and must be stored at 2°C to 8°C (36°F to 46°F). Vials will be provided with latex free stoppers.

MF59® Adjuvant [Microfluoridized Adjuvant 59]

[redacted] The product is available in single-use vial. The vials containing study product must be stored at 2°C to 8°C (36°F to 46°F), protected from light. Do not freeze.

Each of these study products will be labeled according to manufacturer specifications and include the statement "Caution: New Drug Limited by Federal Law to Investigational Use."

Further details are included in the respective, applicable Investigator's Brochures for the Monovalent 2017 H7N9 A/Hong Kong/125/2017 Vaccine (IIV) and package insert for MF59® adjuvant, as well as in the protocol-specific MOP.

Sterile empty vials will be provided with latex-free stoppers.

4.1.2 Product Storage and Stability

The temperature of the storage unit must be manually recorded daily (excluding non-business days and holidays as applicable) and continuously monitored and recorded during the duration of this trial per the participating VTEU site standard operating procedures (SOPs), and documentation will be maintained. If the temperature fluctuates outside of the required range, the affected study product(s) must be quarantined at the correct storage temperature and labeled as 'Do Not Use' (until further notice). The research pharmacist must alert the site PI and study coordinator, if the temperature fluctuates outside of the required range. In the event the temperature fluctuates outside of the required range, including accidental deep-freezing or disruption of the cold chain, the affected study product(s) must not be administered. The site PI or responsible person should immediately contact the DMID Product Support Team at DMIDProductSupportTeam@niaid.nih.gov for further instructions before any additional study vaccinations are administered. Based on the information collected, DMID and/or the manufacturer will determine whether the affected study product(s) can be used. If it cannot be used, the site will receive specific instructions on how to return the affected study product(s) to the DMID CMS or destroy it on site.

4.2 Acquisition/Distribution

2017 H7N9 IIV

2017 H7N9 IIV will be provided by Seqirus under contract to BARDA/DHHS.

MF59® Adjuvant

MF59® will be provided by Seqirus under contract to BARDA/DHHS.

Upon request by DMID, 2017 H7N9 IIV, MF59® adjuvant will be transferred to the following address:

DMID Clinical Materials Services Contract
Fisher BioServices
20439 Seneca Meadows Parkway
Germantown, MD 20876

PBS diluent and sterile empty vials (2-mL, 3-mL or 5-mL) for admixing will be obtained by the DMID Clinical Materials Services (CMS) Contract, Fisher BioServices.

2017 H7N9 IIV, MF59® adjuvant, PBS diluent, and sterile empty vials for study vaccine preparation will be provided through the DMID CMS to the participating VTEU sites prior to the start of this trial upon request and with prior approval from DMID. Should the site PI require additional 2017 H7N9 IIV, MF59® adjuvant, PBS diluent or sterile empty vials during this trial, further instructions are provided in the protocol-specific MOP.

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

Dosage calculations are based on the actual HA content per 0.5 mL. Each 0.5 mL dose of MF59®-adjuvanted study vaccine contains one dose (0.25 mL) of MF59® adjuvant.

See the protocol-specific MOP Appendices for detailed information on the preparation, labeling, storage, and administration of study vaccine for each treatment arm. Study vaccine preparation will be performed by the participating VTEU site research pharmacist on the same day of study vaccine administration.

Visually inspect the 2017 H7N9 IIV, PBS diluent and MF59® adjuvant upon receipt and prior to use. If the study product(s) appear(s) to have been damaged, contaminated or discolored, contain visible particulate matter, or if there are any concerns regarding its integrity, do NOT use the affected study product(s). The affected study product(s) must be quarantined at 2°C to 8°C (36°F to 46°F) and labeled as 'Do Not Use' (until further notice). The site PI or responsible person should immediately contact the DMID Product Support Team at DMIDProductSupportTeam@niaid.nih.gov and DMID Clinical Project Manager for further instructions before any additional study vaccinations are administered. Based on the information collected, DMID and/or the manufacturer will determine whether the affected study product(s) can be used. If it cannot be used, the site will receive specific instructions on how to return the affected study product(s) to the DMID CMS or destroy it on site. If the 2017 H7N9 IIV vaccine PBS diluent or the MF59® adjuvant is unusable, study personnel will use another vial from the

study supply. Replacement vials may be requested by contacting DMID. Additional instructions for quarantine and DMID contact information are provided in the protocol-specific MOP.

For those doses that must be admixed, with PBS diluent, visually inspect the 2017 H7N9 IIV plus PBS diluent admixture (intermediate or final mixed vial depending on treatment arm) prior to use. The 2017 H7N9 IIV plus PBS diluent admixture will be essentially clear and slightly opalescent in color. For those doses that must be admixed with PBS diluent and MF59 adjuvant, visually inspect the 2017 H7N9 IIV/PBS diluent plus MF59 adjuvant admixture (final mixed vial) prior to use. The 2017 H7N9 IIV/plus PBS admixture will be milky (whitish to yellowish) in appearance. If the admixture appears to have been damaged, contaminated or discolored, contain visible particulate matter, or if there are any concerns regarding its integrity, do NOT use the affected admixture. The affected admixture must be quarantined at 2°C to 8°C (36°F to 46°F) for the 2017 H7N9 IIV plus PBS diluent admixture or room temperature for the 2017 H7N9 IIV/PBS diluent plus MF59 adjuvant and labeled as 'Do Not Use' (until further notice). The site PI or responsible person should immediately contact the DMID Product Support Team at DMIDProductSupportTeam@niaid.nih.gov and DMID CPM for further instructions before any additional study vaccinations are administered. Based on the information collected, DMID and/or the manufacturer will determine whether the affected admixture can be used. If it cannot be used, the site will receive specific instructions on how to send the affected admixture to the DMID CMS or destroy it on site. If the affected admixture is unusable, the participating VTEU sites' research pharmacist will prepare another admixture. Additional instructions for quarantine and DMID contact information are provided in the protocol-specific MOP.

For those doses that must be admixed with PBS diluent, the 2017 H7N9 IIV plus PBS diluent admixture, (intermediate or final mixed vial depending on treatment arm), once mixed, must be stored at 2°C to 8°C (36°F to 46°F) in an upright position and must be used within 8 hours. For those doses that must be admixed with PBS diluent and MF59 adjuvant, the 2017 A/H7N9 IIV/PBS diluent plus MF59 adjuvant admixture (final mixed vial), once mixed, must be stored at room temperature in an upright position and must be used within 8 hours.

Only one- 0.5 mL dose of study vaccine should be withdrawn from the intermediate and final mixed vial(s). Gently shake the intermediate and final mixed vial(s) immediately before the single 0.5 mL dose of study vaccine is withdrawn**.**

Study vaccine administration will be performed by an unblinded study personnel member who is credentialed to administer vaccines and may also participate in dose preparation, but will not be involved in study-related assessments or have subject contact for data collection following study vaccine administration. Each dose of study vaccine will be administered via a single IM injection given in the deltoid muscle of the subjects' preferred arm. The site of injection (right or left arm) will be recorded on the appropriate data collection form. Aseptic technique will be used for the withdrawal and administration of each dose of study vaccine using a disposable sterile needle

appropriate in length for each subject and a disposable sterile syringe. See the protocol-specific MOP for information on how to administer IM injections. Each dose of study vaccine must be administered within 30 minutes of drawing into the syringe (not to exceed 8 hours total since admixing time), and the prepared syringe must be stored at room temperature until administered.

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

There will be no dose modifications. If a subject's second study vaccination is deferred, it should be rescheduled to occur within the acceptable protocol-specified window for that visit (Day 22+7 days post first study vaccination). No exceptions to the protocol-specified window will be made.

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

After receipt of the 2017 H7N9 IIV, PBS diluent, MF59® adjuvant, and sterile empty vials, the site PI is responsible for study product distribution and disposition, and has ultimate responsibility for study product accountability. The site PI will delegate to the participating VTEU sites' research pharmacist responsibility for study product accountability. The participating VTEU sites' research pharmacist will be responsible for maintaining complete records and documentation of study product receipt, accountability, dispensation, storage conditions, and final disposition of the study product(s). The study product accountability records and dispensing logs will also capture vial numbers, including final mixed vial number, date of study vaccine preparation/administration, time of study vaccine preparation, expiration of study vaccine preparation, time study vaccine is drawn into the syringe, and amount of study vaccine withdrawn for administration. Time of study vaccine administration to the subject will be captured on the appropriate data collection form. All study product(s), including the amount of 2017 H7N9 IIV, PBS diluent, MF59® adjuvant, and admixture, whether administered or not, must be documented on the appropriate study product accountability record or dispensing log. The sponsor's monitoring staff will verify the participating VTEU sites' study product accountability records and dispensing logs per the site monitoring plan.

Used and unused vials of 2017 H7N9 IIV, PBS diluent, MF59® adjuvant, and admixture will be retained until monitored and released for disposition as applicable. This can occur on an ongoing basis for used vials of 2017 H7N9 IIV, PBS diluent, MF59® adjuvant, and admixture. Used vials of A/H7N9 vaccine, PBS diluent, MF59® adjuvant and admixture may be destroyed in accordance with site-specific SOPs following each monitoring visit where Study Product Accountability is monitored, and resolution of any discrepancies. Final disposition of the unused 2017 H7N9 IIV, PBS diluent, MF59® adjuvant, and sterile empty vials will be determined by

DMID and communicated to the participating VTEU sites by the DMID Clinical Project Manager.

5 SELECTION OF SUBJECTS AND STUDY ENROLLMENT AND WITHDRAWAL

Approximately 371, 18-64 year old males and non-pregnant females who are in good health by history and meet all eligibility criteria, will be enrolled at up to 7 VTEU sites participating in this trial. The target population should reflect the community at large at each of the participating VTEU sites. Estimated time to complete enrollment in this trial is approximately 12 weeks. Information regarding this trial may be provided to potential subjects who have previously participated in vaccine trials conducted at the participating VTEU sites. Other forms and/or mechanisms of recruitment may also be used. The local Institutional Review Board (IRB) will approve all materials prior to use.

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 principal investigator (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.

5.1 Eligibility Criteria

5.1.1 Subject Inclusion Criteria

Subjects eligible to participate in this trial must meet all of the following inclusion criteria:

1. Provide written informed consent prior to initiation of any study procedures.

2. Are able to understand and comply with planned study procedures and be available for all study visits.

3. Are males or non-pregnant females, 18-64 years of age, inclusive.

4. Are in good health[1].

[1] *As determined by physical examination and medical history to evaluate acute or currently ongoing chronic medical diagnoses or conditions, defined as those that have been present for at least 90 days, which would affect the assessment of the safety of subjects or the immunogenicity of study vaccinations. Chronic medical diagnoses or conditions should be stable for the last 60 days (no hospitalizations, ER, or urgent care for condition and no adverse symptoms that need medical intervention such as medication change/supplemental oxygen). This includes no change in chronic prescription medication, dose, or frequency as a result of deterioration of the chronic medical diagnosis or condition in the 60 days prior to enrollment. Any prescription change that is due to change of health care provider, insurance company, etc., or that is done for financial reasons, as long as in the same class of medication, will not be considered a deviation of this inclusion*

*criterion. Any change in prescription medication due to **improvement** of a disease outcome, as determined by the site principal investigator or appropriate sub-investigator, will not be considered a deviation of this inclusion criterion. Subjects may be on chronic or as needed (prn) medications if, in the opinion of the site principal investigator or appropriate sub-investigator, they pose no additional risk to subject safety or assessment of reactogenicity and immunogenicity and do not indicate a worsening of medical diagnosis or condition. Similarly, medication changes subsequent to enrollment and study vaccination are acceptable provided there was no deterioration in the subject's chronic medical condition that necessitated a medication change, and there is no additional risk to the subject or interference with the evaluation of responses to study vaccination. Note: Topical, nasal, and inhaled medications (with the exception of inhaled corticosteroids as outlined in the Subject Exclusion Criteria (see Section 5.1.2), herbals, vitamins, and supplements are permitted.*

5. Oral temperature is less than 100.0°F.
6. Pulse is 47 to 100 bpm, inclusive.
7. Systolic blood pressure is 85 to 150 mmHg, inclusive.
8. Diastolic blood pressure is 55 to 95 mmHg, inclusive.
9. Women of childbearing potential[2] must agree to practice an acceptable contraception method[3] from 30 days before first study vaccination until 60 days after last study vaccination.

[2]*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.*

[3]*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 male or female condoms with spermicide or with the use of applied spermicide, intrauterine devices, NuvaRing®, and licensed hormonal methods such as implants, injectables, or oral contraceptives ("the pill").*

10. Women of childbearing potential must have a negative serum or urine pregnancy test within 24 hours prior to study vaccination.

5.1.2 Subject Exclusion Criteria

Subjects eligible to participate in this trial must not meet any of the following exclusion criteria:

1. Have an acute illness[4], as determined by the site PI or appropriate sub-investigator, within 72 hours prior to study vaccination.

[4]*An acute illness which is nearly resolved with only minor residual symptoms remaining is allowable if, in the opinion of the site principal investigator or appropriate sub-investigator, the residual symptoms will not interfere with the ability to assess safety parameters as required by the protocol.*

2. Have any medical disease or condition that, in the opinion of the site PI or appropriate sub-investigator, is a contraindication to study participation[5].

[5]*Including acute or chronic medical disease or condition, defined as persisting for at least 90 days, 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.*

3. Have immunosuppression as a result of an underlying illness or treatment, a recent history or current use of immunosuppressive or immunomodulating disease therapy.

4. Use of anticancer chemotherapy or radiation therapy (cytotoxic) within 3 years prior to study vaccination.

5. Have known active neoplastic disease or a history of any hematologic malignancy. Non-melanoma, treated, skin cancers are permitted.

6. Have known human immunodeficiency virus (HIV), hepatitis B, or hepatitis C infection.

7. Have known hypersensitivity or allergy to eggs, egg or chicken protein, neomycin, kanamycin, formaldehyde, polysorbate 80, cetyltrimethylammonium bromide (CTAB), squalene-based adjuvants, or other components of the study vaccine.

8. Have a history of severe reactions following previous immunization with licensed or unlicensed influenza vaccines.

9. Have a history of GBS.

10. Have a history of convulsions or encephalomyelitis within 90 days prior to study vaccination.

11. Have a history of PIMMCs[6]

[6]*Refer to Appendix B. List of Potentially Immune Mediated Medical Conditions*

12. Have a history of alcohol or drug abuse within 5 years prior to study vaccination.

13. Have any diagnosis, current or past, of schizophrenia, bipolar disease, or other psychiatric diagnosis that may interfere with subject compliance or safety evaluations.

14. Have been hospitalized for psychiatric illness, history of suicide attempt, or confinement for danger to self or others within 10 years prior to study vaccination.

15. Have taken oral or parenteral (including intra-articular) corticosteroids of any dose within 30 days prior to study vaccination.

16. Have taken high-dose inhaled corticosteroids[7] within 30 days prior to each study vaccination.

[7]*High-dose defined as per age as using inhaled high dose per reference chart https://www.nhlbi.nih.gov/files/docs/guidelines/asthma_qrg.pdf*

17. Received a licensed live vaccine within 30 days prior to the first study vaccination, or plan to receive a licensed live vaccine within 30 days before or after each study vaccination.

18. Received or plan to receive a licensed, inactivated, vaccine (excluding all flu vaccines) within 14 days before or after each study vaccination.

19. Received or plan to receive seasonal IIV within 21 days before or after each study vaccination.

20. Received immunoglobulin or other blood products (with exception of Rho D immunoglobulin) within 90 days prior to each study vaccination.

21. Received an experimental agent[8] within 30 days prior to the first study vaccination, or expect to receive an experimental agent[9] during the 13-month trial-reporting period.

    [8]*Including vaccine, drug, biologic, device, blood product, or medication.*

    [9]*Other than from participation in this trial.*

22. Are participating or plan to participate in another clinical trial with an interventional agent[10] that will be received during the 13-month trial-reporting period.

    [10]*Including licensed or unlicensed vaccine, drug, biologic, device, blood product, or medication.*

23. Received or plan to receive an influenza A/H7 vaccine[11] or have a history of influenza A/H7 subtype infection.

    [11]*And assigned to a group receiving influenza A/H7 vaccine, does not apply to documented placebo recipients.*

24. Have traveled to mainland China and had substantial[12] direct contact with live or freshly slaughtered poultry or pigeons within the past five years.

    [12]*substantial contact is defined as visited a poultry farm and/or a live poultry market.*

25. Occupational exposure to or substantial direct physical contact[13] with birds in the past year and through the 21 days after the second study vaccination.

    [13]*Exposure to free range chickens in the yard is exclusionary. Casual contact with birds at petting zoos or county or state fairs or having pet birds does not exclude subjects from study participation.*

26. Female subjects who are breastfeeding at any given time from the first study vaccination until 30 days after the last study vaccination.

27. Plan to travel outside the US (continental US, Hawaii, and Alaska) from enrollment through 21 days after the second study vaccination.

28. Receipt of Multimeric-001 (M-001) vaccine.

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

5.2.1 Withdrawal from the Study or Discontinuation of the Study Product

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

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

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

- Subject no longer meets eligibility criteria (see Section 5.1 and 8.6.2). Note: Medication changes in the 60 days prior to enrollment, as specified in Subject Inclusion Criterion #4, are exclusionary for receipt of the first study vaccination only. Medication changes subsequent to the first study vaccination are not exclusionary for receipt of the second study vaccination provided there was no deterioration in the subject's chronic medical condition that necessitated a medication change, and there is no additional risk to the subject or interference with the evaluation of responses to study vaccination.
- Subject meets individual halting criteria (see Section 8.6.2).
- Subject becomes noncompliant.
- Subject withdrawal of consent.
- Subject lost to follow-up.
- Termination of this trial.
- Subject becomes pregnant, if applicable.
- New information becomes available that makes further participation unsafe.

- Determined by a physician's discretion to require additional therapy not indicated in the protocol to ensure subject's health and well-being (or treatment failure, if applicable).

- As deemed necessary by the investigator for other reasons.

The primary reason for withdrawal from this trial will be recorded on the Study Status data collection form. Subjects will be encouraged to complete the Early Termination Visit. The Early Termination Visit procedures are listed in Section 6.4.3.

Although subjects are free to withdraw at any time or may be withdrawn by the investigator at any time, those subjects who receive only one dose of study vaccine will be encouraged to remain in this trial for follow-up safety assessments (may be conducted by phone call rather than in person) continuing through approximately 12 months after their last study vaccination. These subjects will also be encouraged to provide a venous blood sample for immunogenicity assays at approximately 7 days and 21 days after their last study vaccination, if applicable. See the protocol-specific Manual of Procedures (MOP) for alternate follow-up requirements.

Every attempt will be made to follow all AEs, including solicited injection site and systemic reactions, unsolicited non-serious AEs, SAEs, MAAEs, including NOCMCs, and PIMMCs, ongoing at the time of early withdrawal through resolution as per applicable collection times defined for the specific type of AE.

In the case of subjects who fail to appear for a follow-up safety assessment, efforts (i.e., three documented contact attempts via phone calls 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.

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

5.2.2 Subject Replacement

Subjects who sign the informed consent form (ICF), and are randomized and vaccinated, and subsequently withdraw, or are withdrawn or terminated from this study, or are lost to follow-up will not be replaced. If subjects withdraw, or are withdrawn or terminated from the study, or are lost to follow-up after signing the ICF and randomization but before receipt of study vaccine, additional subjects may be enrolled and randomized for replacement.

5.2.3 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.

6 STUDY PROCEDURES

Complete study schedule details listed by type of visit are described below. Refer also to APPENDIX A: SCHEDULE OF PROCEDURES AND EVALUATIONS.

6.1 Screening (Optional) Visit 00, Day -28 to -1, Clinic Visit

- 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 administration of the first study vaccination.
- Demographic information will be obtained by interview of subjects.
- Eligibility criteria will be reviewed with subjects.
- Complete medical history will be obtained by interview of subjects to ensure eligibility.
- All concomitant medications taken within 60 days prior to signing the ICF will be reviewed with subjects to determine stability of chronic diseases and eligibility. Medications reported in the eCRF are limited to those taken within 30 days prior to the first study vaccination.
- Subject receipt of licensed seasonal influenza vaccine over the current (2018-2019) and previous two seasons (2016-2017 and 2017-2018), what type (inactivated or live attenuated), and approximate date of vaccination will be recorded on the appropriate data collection form, if known. Prior receipt of licensed seasonal influenza vaccine is not exclusionary, as long as it has been administered within the allowable window (see Section 5.1.2).
- Subject receipt of non-seasonal influenza vaccines, including those that are experimental, what type (inactivated or live attenuated), what subtype (e.g., A/H3, A/H5, A/H9) and approximate date of vaccination will be recorded on the appropriate DCF, if known. Prior receipt of non-seasonal influenza vaccines are not exclusionary, except influenza A/H7 vaccines (see Section 5.1.2).
- Vital signs, including oral temperature, pulse, and blood pressure, will be obtained to ensure eligibility prior to first study vaccination. 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 the calculation of BMI.

- A physical examination will be performed on all subjects to include the following organs and organ systems: skin, head and neck, lungs, heart, liver, spleen, extremities, lymph nodes, abdomen, general appearance, musculoskeletal, and nervous system and as assessment for signs suggestive of a PIMMC, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.

- A serum or urine pregnancy test may be performed on all women of childbearing potential. Results must be negative to ensure eligibility.

6.2 Enrollment, Visit 01 Day 01 for subjects previously screened at Day -28 to -1 and First Vaccination (Dose 1), Clinic Visit

- Subject's willingness to participate will be reconfirmed and documented in the subject's study records prior to performing any further study procedures, including administration of the first study vaccination.

- Eligibility criteria will be reviewed prior to administration of the first study vaccination to ensure continued eligibility.

- Interim medical history, including an assessment for new medical conditions, stability of chronic diseases, and symptoms suggestive of PIMMCs, will be obtained by interview of subjects prior to the study vaccination and any changes since the previous clinic visit or contact will be noted.

- All concomitant medications will be reviewed with subjects prior to the first study vaccination for accuracy and completeness. Any new concomitant medications taken since the screening visit will be reviewed with subjects and assessed for continued eligibility prior to the first study vaccination.

- Vital signs, including oral temperature, pulse, and blood pressure, will be obtained to ensure eligibility prior to first study vaccination. Vital signs assessed on Day 1 prior to the first 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.

- A targeted physical examination, including an assessment for signs suggestive of PIMMCs, may be performed prior to the first study vaccination, if indicated based on review of complete medical history and any updates obtained by interview of subjects since the screening visit, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.

- A serum or urine pregnancy test will be performed within 24 hours prior to the first study vaccination on all women of childbearing potential. Results must be negative and known prior to randomization and first study vaccination.

- Subjects will be enrolled in AdvantageEDC℠ and assigned randomly to a treatment arm prior to the first study vaccination.

- Pre-administration reactogenicity assessments will be performed prior to the first study vaccination to establish baseline.

- Approximately 10 mL of venous blood will be collected immediately prior to the first study vaccination for baseline serum antibody assays.

- Approximately 10 mL of venous blood will be collected immediately prior to the first study vaccination for baseline clinical safety labs (WBC, Hgb, PLT, ALT, T. Bili, and Cr), and performed by the central (clinical) laboratory. The results from this blood draw will not be available or reviewed prior to study vaccination, and will serve as a safety baseline assessment only.

- Approximately 10 mL of venous blood will be collected prior to study vaccination for future research from subjects who consent to collection of serum for future use either by signing an ICF that includes collection of future use samples as a condition of study participation or by indicating that they can opt in to sample collection for future use if the ICF allows the option to choose that option.

- Subjects will then receive a single dose of study vaccine via IM injection into the deltoid muscle of the preferred arm. The site of injection (right or left arm) and time of administration will be recorded on the appropriate data collection form. Subjects will be observed in the clinic for at least 20 minutes after the first study vaccination. The first study vaccination site will be examined, post-administration reactogenicity assessments will be performed, and any AE/SAEs will be recorded on the appropriate data collection form prior to discharge from the clinic.

- Subjects will be provided with a Memory Aid and other study-related materials to record daily oral temperature, solicited injection site and systemic reactions, any unsolicited AEs, and concomitant medications. 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 on how to use their Memory Aid and how to measure and record AEs prior to discharge from the clinic. Subjects will be instructed to notify the study center if they develop any severe reactions after the first 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.

- Subjects may be re-screened if they have an acute illness, present with scheduling conflicts, have abnormal vital sign(s), or have any other issue that the investigator thinks is acceptable to postpone receipt of study product to another date.

6.3 Visit 01, Day 1, Enrollment/Baseline (for subjects not previously screened at Day -28 to -1) and First Study Vaccination (Dose 1), Clinic Visit

- 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 administration of the first study vaccination.

- Demographic information will be obtained by interview of subjects.

- Complete medical history will be obtained by interview of subjects prior to the first study vaccination to ensure eligibility.

- All concomitant medications taken within 60 days prior to signing the ICF will be reviewed with subjects. Medications reported in the eCRF are limited to those taken within 30 days prior to the first study vaccination.

- Subject receipt of licensed seasonal influenza vaccine over the current (2018-2019) and previous two seasons (2016-2017 and 2017-2018), what type (inactivated or live attenuated), and approximate date of vaccination will be recorded on the appropriate data collection form, if known. Prior receipt of licensed seasonal influenza vaccine is not exclusionary, as long as it has been administered within the allowable window (see Section 5.1.2).

- Subject receipt of non-seasonal influenza vaccines, including those that are experimental, what type (inactivated or live attenuated), what subtype (e.g., A/H3, A/H5, A/H9) and approximate date of vaccination will be recorded on the appropriate DCF, if known. Prior receipt of non-seasonal influenza vaccines are not exclusionary, except influenza A/H7 vaccines (see Section 5.1.2).

- Vital signs, including oral temperature, pulse, and blood pressure, will be obtained to ensure eligibility prior to first study vaccination. Vital signs assessed on Day 1 prior to the first 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.

- Height and weight will be collected prior to the first study vaccination for the calculation of BMI.

- A physical examination will be performed on all subjects to include the following organs and organ systems: skin, head and neck, lungs, heart, liver, spleen, extremities, lymph nodes, abdomen, general appearance, musculoskeletal and nervous system and as assessment for signs suggestive of a PIMMC, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.

- Eligibility criteria will be reviewed with subjects prior to the first study vaccination to ensure continued eligibility.

- A serum or urine pregnancy test will be performed within 24 hours prior to the first study vaccination on all women of childbearing potential. Results must be negative and known prior to randomization and first study vaccination.

- Subjects will be enrolled in AdvantageEDC^{SM} and assigned randomly to a treatment arm prior to the first study vaccination.

- Pre-administration reactogenicity assessments will be performed prior to the first study vaccination to establish baseline.

- Approximately 10 mL of venous blood will be collected immediately prior to the first study vaccination for baseline serum antibody assays.

- Approximately 10 mL of venous blood will be collected immediately prior to the first study vaccination for baseline clinical safety labs (WBC, Hgb, PLT, ALT, T. Bili, and Cr), and performed by the central (clinical) laboratory. The results from this blood draw will not be available or reviewed prior to study vaccination, and will serve as a safety baseline assessment only.

- Approximately 10 mL of venous blood will be collected prior to study vaccination for future research from subjects who consent to collection of serum for future use, either by signing an ICF that includes collection of future use samples as a condition of study participation or by indicating that they opt in to sample collection for future use if the ICF allows the option to choose that option.

- Subjects will then receive a single dose of study vaccine via IM injection into the deltoid muscle of the preferred arm. The site of injection (right or left arm) and time of administration will be recorded on the appropriate data collection form. Subjects will be observed in the clinic for at least 20 minutes after the first study vaccination. The first study

vaccination site will be examined, post-administration reactogenicity assessments will be performed, and any AE/SAEs will be recorded on the appropriate data collection form prior to discharge from the clinic.

- Subjects will be provided with a Memory Aid and other study-related materials to record daily oral temperature, solicited injection site and systemic reactions, any unsolicited AEs, and concomitant medications. 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 on how to use their Memory Aid and how to measure and record AEs prior to discharge from the clinic. Subjects will be instructed to notify the study center if they develop any severe reactions after the first study vaccination. If the site principal investigator 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.

6.4 Planned Study Visits

6.4.1 Follow-up

Follow-up visits are scheduled in reference to study vaccination dates as indicated for each visit window.

Visit 02, Day 4, Memory Aid Review, Phone Call
(Window: Day 4±1 days post first study vaccination)

Study personnel will contact subjects by phone to solicit any AEs/SAEs/MAAEs/NOCMCs/PIMMCs, medical history, and concomitant medication information and review information on their Memory Aid. Based on the information, subjects may be asked to return to the clinic for evaluation.

Visit 03, Day 8, Clinic Visit
(Window: Day 8+2 days post first study vaccination)

- Interim medical history, including an assessment for new medical conditions, stability of chronic diseases, and symptoms suggestive of PIMMCs, will be obtained by interview of subjects and any changes since the previous clinic visit or contact will be noted.

- Memory Aid information will be reviewed with subjects.

- All concomitant medications (including solicitation for receipt of any non-study influenza vaccines), including those that are experimental, what type (inactivated or live attenuated), what subtype (e.g., A/H3, A/H5, A/H9) and approximate date of vaccination will be recorded on the appropriate DCF, if known and not previously collected).

- All AE/SAEs/MAAEs/NOCMCs/PIMMCs will be recorded on the appropriate data collection form.

- A targeted physical examination, including an assessment for signs suggestive of PIMMCs, may be performed, if indicated based on review of interim medical history, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.

- The first study vaccination site will be examined.

- Approximately 10 mL of venous blood will be collected for clinical safety labs (WBC, Hgb, PLT, ALT, T. Bili, Cr), and performed by the central (clinical) laboratory.

- Approximately 10 mL of venous blood will be collected for serum antibody assays.

- Approximately 10 mL of venous blood will be collected for future research from subjects who consent to collection of serum for future use either by signing an ICF that includes collection of future use samples as a condition of study participation or by indicating that they can opt in to sample collection for future use if the ICF allows the option to choose that option.

Visit 04, Day 22, Second Study Vaccination (Dose 2), Clinic Visit
(Window: Day 22+7 days post first study vaccination)

- Eligibility criteria will be reviewed with subjects prior to the second study vaccination to ensure continued eligibility.

- For a subject to receive the second study vaccination, refer to section 8.6.2 for second vaccination eligibility criteria.

- Interim medical history, including an assessment for new medical conditions, stability of chronic diseases, and symptoms suggestive of PIMMCs, will be obtained by interview of subjects prior to the second study vaccination and any changes since the previous clinic visit or contact will be noted.

- All concomitant medications (including solicitation for receipt of any non-study influenza vaccines), including those that are experimental, what type (inactivated or live attenuated), what subtype (e.g., A/H3, A/H5, A/H9) and approximate date of vaccination will be recorded on the appropriate DCF, if known and not previously collected. Prior receipt of non-seasonal influenza vaccines are not exclusionary, except influenza A/H7 vaccines (see Section 5.1.2) will be recorded on the appropriate data collection form prior to the second study vaccination.

- All AEs/SAEs/MAAEs/NOCMCs/PIMMCs will be recorded on the appropriate data collection form.

- Vital signs, including oral temperature, pulse, and blood pressure, will be obtained prior to the second study vaccination. Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature. Note: Vital signs are not required for subjects who are discontinued from receipt of the second study vaccination and are being followed for safety.

- A targeted physical examination, including an assessment for signs suggestive of PIMMCs, may be performed prior to the second study vaccination, if indicated based on review of interim medical history, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.

- A serum or urine pregnancy test will be performed within 24 hours prior to the second study vaccination on all women of childbearing potential. Results must be negative and known prior to the second study vaccination.

- Pre-administration reactogenicity assessments will be performed prior to the second study vaccination to establish baseline.

- Approximately 10 mL of venous blood will be collected immediately prior to the second study vaccination for clinical safety labs (WBC, Hgb, PLT, ALT, T. Bili, and Cr), and performed by the central (clinical) laboratory. The results from this blood draw will not be available or reviewed prior to study vaccination.

- Approximately 10 mL of venous blood will be collected immediately prior to the second study vaccination for serum antibody assays.

- Approximately 10 mL of venous blood will be collected immediately prior to the second study vaccination for future research from subjects who consent to collection of serum for future use either by signing an ICF that includes collection of future use samples as a

condition of study participation or by indicating that they can opt in to sample collection for future use if the ICF allows the option to choose that option.

- Subjects will then receive a single dose of study vaccine via IM injection into the deltoid muscle of the preferred arm. The second study vaccination may be given in the same preferred arm as long as there is no interference with the reactogenicity assessment. The site of injection (right or left arm) and time of administration will be recorded on the appropriate data collection form. Subjects will be observed in the clinic for at least 20 minutes after the second study vaccination. The second study vaccination site will be examined, post-administration reactogenicity assessments will be performed, and any AE/SAEs will be recorded on the appropriate data collection form prior to discharge from the clinic.

- Subjects will be provided with a Memory Aid and other study-related materials to record daily oral temperature, solicited injection site and systemic reactions, any unsolicited AEs, and concomitant medications. 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 on how to use their Memory Aid and how to measure and record AEs prior to discharge from the clinic. Subjects will be instructed to notify the study center if they develop any severe reactions after the second 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.

Visit 05, Day 25, Memory Aid Review, Phone Call
(Window: Day 4 ±1 days post second study vaccination)

Study personnel will contact subjects by phone to solicit any AE/SAE, medical history, and concomitant medication information (including solicitation for receipt of any non-study influenza vaccines), including those that are experimental, what type (inactivated or live attenuated), what subtype (e.g., A/H3, A/H5, A/H9) and approximate date of vaccination will be recorded on the appropriate DCF, if known and not previously collected) and review information on their Memory Aid. Based on the information, subjects may be asked to return to the clinic for evaluation. Note: For subjects who are discontinued from the receipt of the second study vaccination, AEs will be limited to SAEs, MAAEs, including NOCMCs, and PIMMCs.

Visit 06, Day 29, Clinic Visit
(Window: Day 8+2 days post second study vaccination)

- Interim medical history, including an assessment for new medical conditions, stability of chronic diseases, and symptoms suggestive of PIMMCs, will be obtained by interview of subjects and any changes since the previous clinic visit or contact will be noted.

- Memory Aid information will be reviewed with subjects.

- All concomitant medications (including solicitation for receipt of any non-study influenza vaccines), including those that are experimental, what type (inactivated or live attenuated), what subtype (e.g., A/H3, A/H5, A/H9) and approximate date of vaccination will be recorded on the appropriate DCF, if known and not previously collected).

- All AE/SAEs will be recorded on the appropriate data collection form. Note: for subjects who discontinued from the receipt of the second study vaccination, AEs will be limited to SAEs, MAAEs, including NOCMCs, and PIMMCs.

- A targeted physical examination, including an assessment for signs suggestive of PIMMCs, may be performed, if indicated based on review of interim medical history, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.

- The second study vaccination site will be examined.

- Approximately 10 mL of venous blood will be collected for clinical safety labs (WBC, Hgb, PLT, ALT, T. Bili, and Cr), and performed by the central (clinical) laboratory.

- Approximately 10 mL of venous blood will be collected for serum antibody assays.

- Approximately 10 mL of venous blood will be collected for future research from subjects who consent to collection of serum for future use either by signing an ICF that includes collection of future use samples as a condition of study participation or by indicating that they can opt in to sample collection for future use if the ICF allows the option to choose that option.

Visit 07, Day 43, Clinic Visit
(Window: Day 22+7 days post second study vaccination)

- Interim medical history, including an assessment for new medical conditions, stability of chronic diseases, and symptoms suggestive of PIMMCs, will be obtained by interview of subjects and any changes since the previous clinic visit or contact will be noted.

- All concomitant medications (including solicitation for receipt of any non-study influenza vaccines), including those that are experimental, what type (inactivated or live attenuated), what subtype (e.g., A/H3, A/H5, A/H9) and approximate date of vaccination will be recorded on the appropriate DCF, if known and not previously collected).

- All AE/SAEs will be recorded on the appropriate data collection form. Note: for subjects who discontinued from the receipt of the second study vaccination, AEs will be limited to SAEs, MAAEs, including NOCMCs, and PIMMCs.

- A targeted physical examination, including an assessment for signs suggestive of PIMMCs, may be performed, if indicated based on review of interim medical history, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.

- Approximately 10 mL of venous blood will be collected for serum antibody assays.

- Approximately 10 mL of venous blood will be collected for future research from subjects who consent to collection of serum for future use either by signing an ICF that includes collection of future use samples as a condition of study participation or by indicating that they can opt in to sample collection for future use if the ICF allows the option to choose that option.

Visit 08, Day 82, Safety Follow-up, Phone Call
(Window: Day 61±7 days post second study vaccination)

Subjects will be contacted by phone to query for safety events and solicitation for receipt of all concomitant medications (including any solicitation for receipt of any non-study influenza vaccines), including those that are experimental, what type (inactivated or live attenuated), what subtype (e.g., A/H3, A/H5, A/H9) and approximate date of vaccination will be recorded on the appropriate DCF, if known and not previously collected. Adverse events limited to MAAEs including NOCMCs, PIMMCs, and SAEs that have occurred since the previous clinic visit or contact will be solicited. Based on the information, subjects may be asked to return to the clinic for evaluation.

Visit 09, Day 142, Safety Follow-up, Phone Call
(Window: Day 121±14 days post second study vaccination)

Subjects will be contacted by phone to query for safety events and solicitation for receipt of all concomitant medications (including any solicitation for receipt of any non-study influenza vaccines), including those that are experimental, what type (inactivated or live attenuated), what subtype (e.g., A/H3, A/H5, A/H9) and approximate date of vaccination will be recorded on the appropriate DCF, if known and not previously collected. Adverse events limited to MAAEs including NOCMCs, PIMMCs, and SAEs that have occurred since the previous clinic visit or contact will be solicited. Based on the information, subjects may be asked to return to the clinic for evaluation.

Visit 10, Day 202, Safety Follow-up, Clinic Visit
(Window: Day 181±14 days post second study vaccination)

- Interim medical history, including an assessment for new medical conditions, stability of chronic medical diseases, and symptoms suggestive of PIMMCs, will be obtained by interview of subjects and any changes since the previous clinic visit or contact will be noted.

- All concomitant medications (including solicitation for receipt of any non-study influenza vaccines), including those that are experimental, what type (inactivated or live attenuated), what subtype (e.g., A/H3, A/H5, A/H9) and approximate date of vaccination will be recorded on the appropriate DCF, if known and not previously collected).

- Adverse events limited to MAAEs including NOCMCs, PIMMCs, and SAEs that have occurred since the previous clinic visit or contact will be solicited.

- A targeted physical examination, including an assessment for signs suggestive of PIMMCs, may be performed, if indicated based on review of interim medical history, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.

- Approximately 10 mL of venous blood will be collected for serum antibody assays.

- Approximately 10 mL of venous blood will be collected for future research from subjects who consent to collection of serum for future use either by signing an ICF that includes collection of future use samples as a condition of study participation or by indicating that they can opt in to sample collection for future use if the ICF allows the option to choose that option.

6.4.2 Final Study Visit, Visit 11, Day 387, Safety Follow-up, Phone Call (Window: Day 366±14 days post second study vaccination)

Subjects will be contacted by phone to query for safety events. AEs limited to MAAEs including NOCMCs, and PIMMCS, and SAEs that have occurred since the previous clinic visit or contact will be solicited. Based on the information, subjects may be asked to return to the clinic for evaluation.

6.4.3 Early Termination Visit (if needed)

The following activities will be performed at the early termination visit on subjects who withdraw, or are withdrawn or terminated from this trial:

- Interim medical history, including an assessment for new medical conditions and symptoms suggestive of PIMMCs, will be obtained by interview of subjects and any changes since the previous clinic visit or contact will be noted.

- Memory Aid information will be reviewed with subjects (if within 7 days after the last study vaccination).

- All concomitant medications will be recorded on the appropriate data collection form (if within 180 days after the last study vaccination, including those that are experimental, what type (inactivated or live attenuated), what subtype (e.g., A/H3, A/H5, A/H9) and approximate date of vaccination will be recorded on the appropriate DCF, if known and not previously collected). Receipt of any non-study influenza vaccine will be recorded if within 180 days after the last study vaccination.

- Unsolicited non-serious AEs will be documented and reported from the time of each study vaccination through approximately 21 days after each study vaccination. SAEs, MAAEs, including NOCMCs, and PIMMCs will be documented and reported from the time of the first study vaccination through approximately 12 months after last study vaccination).

- Vital signs, including oral temperature, pulse, and blood pressure, may be obtained if indicated. Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature.

- A targeted physical examination, including an assessment for signs suggestive of PIMMCs, may be performed, if indicated based on review of interim medical history, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.

- The study vaccination site will be examined (if within 7 days after the last study vaccination).

- Post-administration reactogenicity assessments will be performed (if within 7 days after the last study vaccination).

- Approximately 10 mL of venous blood will be collected for serum antibody assays (if within 21 days after the last study vaccination).

- Approximately 10 mL of venous blood will be collected for clinical safety labs (WBC, Hgb, PLT, ALT, T. Bili, and Cr), and performed by the central (clinical) laboratory if done within 7 days after the last study vaccination.

- Approximately 10 mL of venous blood will be collected for future research (if within 21 days after the last study vaccination) from subjects who consent to collection of serum for future use either by signing an ICF that includes collection of future use samples as a condition of study participation or by indicating that they can opt in to sample collection for future use if the ICF allows the option to choose that option.

6.5 Unscheduled Visit (if needed)

Unscheduled visits may occur at any time during this trial. Any of the following activities may be performed:

- Interim medical history, including an assessment for new medical conditions and symptoms suggestive of PIMMCs, will be obtained by interview of subjects and any changes since the previous clinic visit or contact will be noted (if indicated).

- Memory Aid information will be reviewed with subjects (if within 7 days after the last study vaccination).

- All concomitant medications will be recorded on the appropriate data collection form (if within 180 days after the last study vaccination). Receipt of any non-study influenza vaccine, including those that are experimental, what type (inactivated or live attenuated), what subtype (e.g., A/H3, A/H5, A/H9) and approximate date of vaccination will be recorded on the appropriate DCF, if known and not previously collected will be recorded if within 180 days after the last study vaccination.

- Unsolicited non-serious AEs will be documented and reported from the time of each study vaccination through approximately 21 days after each study vaccination. SAEs, MAAEs, including NOCMCs, and PIMMCs will be documented and reported from the time of the first study vaccination through approximately 12 months after the last study vaccination.

- Vital signs, including oral temperature, pulse, and blood pressure, may be obtained if indicated. Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature.

- A targeted physical examination, including an assessment for signs suggestive of PIMMCs, may be performed, if indicated based on review of interim medical history, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.

- The study vaccination site will be examined (if within 7 days after the last study vaccination).

- Post-administration reactogenicity assessments will be performed (if within 7 days after the last study vaccination).

- Approximately 10 mL of venous blood will be collected for serum antibody assays (if within 21 days after the last study vaccination).

- Approximately 10 mL of venous blood will be collected for clinical safety labs (WBC, Hgb, PLT, ALT, T. Bili, and Cr), and performed by the central (clinical) laboratory if indicated.

- Approximately 10 mL of venous blood will be collected for future research from subjects who consent to collection of serum for future use (if within 21 days after the last study vaccination) either by signing an ICF that includes collection of future use samples as a condition of study participation or by indicating that they can opt in to sample collection for future use if the ICF allows the option to choose that option.

6.6 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, 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 deviations, or within five working days of the scheduled protocol-required activity. All deviations must be promptly reported to DMID per the SDCC protocol deviation reporting procedures.

All deviations, as defined above, must be addressed in study subject data collection forms. A completed copy of the DMID Protocol Deviation Form must be maintained in the regulatory file, as well as 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

7 DESCRIPTION OF CLINICAL AND LABORATORY EVALUATIONS

7.1 Clinical Evaluations

Complete medical history will be obtained by interview of subjects at the screening visit (optional) or on Day 1 prior to the first study vaccination. Subjects will be queried regarding a history of significant medical disorders of the head, eyes, ears, nose, throat, mouth, cardiovascular system, lungs, gastrointestinal tract, liver, pancreas, kidney, urologic system, nervous system, blood, lymph nodes, endocrine system, musculoskeletal system, skin, and genital/reproductive tract. A history of any allergies, cancer, immunodeficiency, psychiatric illness, substance abuse, and autoimmune disease will be solicited. At follow-up visits after the first study vaccination, an interim medical history will be obtained by interview of subjects noting any changes since the previous clinic visit or contact. The interim medical history should include an assessment for new medical conditions and symptoms suggestive of PIMMCs.

Concomitant medications will be collected as described in Section 7.1.1.

At the screening visit (optional) or the baseline visit (Day 1) a physical examination will be performed on all subjects to include the following organs and organ systems: including skin, head and neck, lungs, heart, liver, spleen, extremities, lymph nodes, abdomen, general appearance, musculoskeletal, and nervous system, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator. At follow-up visits after the first study vaccination, a targeted physical examination may be performed, if indicated based on the subject's interim medical history, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator. Targeted physical examinations should also include an assessment for signs suggestive of PIMMCs.

Vital signs (oral temperature, pulse, and blood pressure) will be collected at the screening visit (optional) and prior to each study vaccination (Days 1 and 22). Vital signs assessed on Day 1 prior to the first 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.

Height and weight will be collected at the screening visit (optional) or on Day 1 prior to the first study vaccination for the calculation of BMI.

Reactogenicity assessments will include an assessment of solicited AEs occurring from the time of each study vaccination through Day 8 after each study vaccination, which includes an assessment of injection site reactions including pruritus, ecchymosis, erythema, induration/ swelling, pain, and tenderness as well as systemic reactions including fever, feverishness,

fatigue, malaise, myalgia, arthralgia, headache, and nausea. Pre-administration reactogenicity assessments will be performed prior to each study vaccination to establish baseline, then the study vaccination will be given.

Subjects will be observed in the clinic for at least 20 minutes after each 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 data collection form prior to discharge from the clinic. The study vaccination site will also be examined approximately 7 days after each study vaccination.

All subjects will complete a subject Memory Aid from the time of each study vaccination through 7 days after each study vaccination. Subject Memory Aids will be reviewed with the subjects for AEs (solicited injection site and systemic reactions and unsolicited AEs) approximately 3 and 7 days after each study vaccination via phone call (Day 4) and clinical visit (Day 8).

7.1.1 Assessment of Concomitant Medications/Treatments other than Study Product

Administration of any medications, therapies, or vaccines will be recorded on the appropriate data collection form. Concomitant medications will include all current medications and medications taken in the 60 days prior to signing the ICF through approximately 180 days after the last study vaccination or early termination (if prior to 180 days after the last study vaccination), whichever occurs first. Medications reported in the electronic case report form (eCRF) are limited to those taken within 30 days prior to the first study vaccination through approximately 180 days after the last study vaccination. Prescription and over-the-counter drugs will be included as well as herbals, vitamins, and supplements. In addition, receipt of non-study influenza vaccines will be solicited through approximately 180 days after the last study vaccination, and reported in the eCRF. Use of a new medication should prompt evaluation for the occurrence of any MAAE, including a new diagnosis of chronic medical disease or condition.

Medications that might interfere with the evaluation of the investigational product(s) should not be used during the trial-reporting period (approximately 12 months after the last study vaccination) unless clinically indicated as part of the subject's health care. Medications in this category include the prohibited medications per the Subject Exclusion Criteria (see Section 5.1.2). In addition, the site PI or appropriate sub-investigator may identify other medications that should not be used due to a risk to subject safety or assessment of reactogenicity and immunogenicity.

7.2 Laboratory Evaluations

7.2.1 Clinical Laboratory Evaluations

Serum or urine pregnancy tests will be performed. Serum or urine pregnancy tests will be performed locally by site laboratory. Pregnancy testing will be done at the screening visit (optional) and within 24 hours prior to each study vaccination on all women of childbearing potential. Results must be negative and known prior to randomization on Day 1 and administration of each study vaccination to be eligible for participation in this trial and receipt of each study vaccination.

Clinical safety laboratory parameters (WBC, Hgb, PLT, ALT, T. Bili, and Cr) will be collected from each subject prior to each study vaccination and approximately 7 days after each study vaccination. These evaluations will be performed by the central (clinical) laboratory. Venous blood samples (approximately 10 mL) will be collected for these safety labs. The results from the clinical safety laboratory parameters collected on Day 1 will not be available or reviewed prior to study vaccination, and will serve as a safety baseline assessment only.

The volume of venous blood to be collected for the clinical safety laboratory evaluations is presented in Table 2.

7.2.2 Research Assays

Immunogenicity

Assays to determine serum levels of HAI and Neut antibodies will be performed at Southern Research. Venous blood samples (approximately 10 mL) for antibody assays will be collected from each subject immediately prior to each study vaccination (Day 1 and approximately Day 22) and, approximately 7 days after each study vaccination (approximately Day 8 and Day 29), and approximately 21 days and 180 days after the second study vaccination (approximately Days 43 and 202). Subjects who withdraw early will have HAI and Neut antibody assays run on available sera.

Venous blood samples (10 mL) will also be collected for future use at the same time points. Sites may elect to allow subjects to consent to study participation but to have the option to opt in for the collection of the future use samples, or may include collection of future use samples as a condition of study participation and not allow the option.

The assays for determination of the NA content and antibodies to the NA are under development. If successful, the correlation of NA content in the 2017 H7N9 IIV with elicited N9 NA-specific serum antibody responses may be assessed; no additional venous blood will be collected from

subjects. 2017 H7N9 IIV and adjuvant will be shipped from the DMID CMS to the NA content assay-designated laboratory for NA content assessment. Any laboratory involved with the determination of NA content or NA-specific antibody responses will remain blinded to the HAI and Neut antibodies results performed at Southern Research.

The volume of venous blood to be collected for immunogenicity assays and future research is presented in Table 2.

Table 2: Venipuncture Volumes (mL):

Study Visit Number	**V01**	**V03**	**V04**	**V06**	**V07**	**V10**	**Total (mL)**
Study Day post first study vaccination	**Enrollment and Dose 1 D1**	**D8+2d**	**D22+7d**	***D29***	***D43***	***D202***	
Study Day post second study vaccination			**Dose 2 D1**	**D8+2d**	**D22+7d**	**D181±14d**	
Study Vaccination	X		X				
Clinical Baseline and Safety Laboratory Evaluations~	10†	10	10†	10			**40**
Immunogenicity Assays	10†	10	10†	10	10	10	**60**
Serum Sample for Future Research#	10†	10	10†	10	10	10	**60**
Total (mL)	**30**	**30**	**30**	**30**	**20**	**20**	**160**

#Sites may elect to allow subjects to consent to study participation but to have the option to opt in for the collection of the future use samples, or may include collection of future use samples as a condition of study participation and not allow the option.

†All blood drawn immediately prior to study vaccination.

7.2.2.1 Laboratory Specimen Preparation, Handling, and Shipping

Instructions for specimen preparation, handling, and storage are included in the central (clinical) laboratory manual and protocol-specific MOP as appropriate.

7.2.2.2 Laboratory Specimen Shipment

Specimen shipment will occur at intervals during the course of this trial following all applicable International Air Transport Association (IATA) requirements and according to the specifics for storage temperature and documentation as detailed in the central (clinical) laboratory manual and protocol-specific MOP as appropriate.

Specimens for safety laboratory evaluations will be shipped from the participating VTEU sites to the central (clinical) laboratory.

Specimens for HAI and Neut antibody assays will be shipped from the participating VTEU sites to the DMID CMS, and then provided by the DMID CMS to Southern Research in a blinded manner.

Specimens for the NA antibody assays will be shipped from the participating VTEU sites to the DMID CMS, and then provided by the DMID CMS to the NA antibody assay laboratory once it has been identified.

Further instructions for specimen shipment are included in the central (clinical) laboratory manual and protocol-specific MOP, as appropriate.

8 ASSESSMENT OF SAFETY

8.1 Assessing and Recording Safety Parameters

Safety will be assessed by the frequency and severity of:

1. SAEs occurring from the time of the first study vaccination through approximately 12 months after the last study vaccination.

2. Solicited AEs – reactogenicity events occurring from the time of each study vaccination through 7 days after each study vaccination:

   a) Injection site reactions including pruritus, ecchymosis, erythema, induration/swelling, pain, and tenderness.

   b) Systemic reactions including fever, feverishness, fatigue, malaise, myalgia, arthralgia, headache, and nausea.

3. Clinical safety laboratory AEs occurring from the time of each study vaccination through approximately 7 days after each study vaccination. Parameters to be evaluated include WBC, Hgb, PLT, ALT, T. Bili, and Cr.

4. Unsolicited AEs – non-serious AEs occurring from the time of each study vaccination through approximately 21 days after each study vaccination.

5. MAAEs, including NOCMCs, and PIMMCs occurring from the time of the first study vaccination through approximately 12 months after the last study vaccination.

8.1.1 Adverse Events

Adverse Event (AE): (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 or not 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 a 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 data collection form and eCRF. Information to be collected for AEs includes event description, date of onset, 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), 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 unsolicited AE. However, if the severity or frequency of any pre-existing medical condition increases, it will be recorded as an unsolicited AE.

If an event meets both the criteria of a study endpoint and an adverse event, the event will be reported either as a study endpoint or as an adverse event (not both).

8.1.1.1 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 data collection form and 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). For events not included in the protocol-defined grading system, the following guidelines will be used to quantify severity:

- Mild (Grade 1): Events require minimal or no treatment and do not interfere with the subject's daily activities.
- Moderate (Grade 2): Events result in a low level of inconvenience or concern with therapeutic measures. Moderate events may cause some interference with functioning and daily activities.
- Severe (Grade 3): Events interrupt the subject's daily activities and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Changes in the severity of an AE should be documented to allow for assessment of the duration of the event at each level of intensity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Relationship to Study Product: The assessment of the relationship of an AE to the administration of study product is made only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as an investigator based on all available information at the time of the completion of the eCRF. 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. To help assess, the following guidelines are used:

- 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.

8.1.2 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 – hurts only when injection site is touched or the arm is moved	The area immediately surrounding the injection site hurts only when touched or with arm motion, **and** it does **not**	The area immediately surrounding the injection site hurts when touched or with arm motion, **and** it interferes with daily activity	The area immediately surrounding the injection site hurts when touched or with arm motion, **and** it prevents daily activity

Injection Site Reaction	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
	interfere with daily activity		
Pruritus (Itching)	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
Ecchymosis	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
Erythema	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
Induration/Swelling	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity

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

Table 4: Injection Site Reactogenicity Measurements

Injection Site Reaction	Small	Medium	Large
Ecchymosis*	<20 mm	20 mm – 50 mm	>50 mm
Erythema*	<20 mm	20 mm – 50 mm	>50 mm
Induration/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
Arthralgia *	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)
Headache	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Nausea	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity

* Not at injection site.

Oral temperature[#] will be graded as follows:

Table 6: Quantitative Systemic 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.

Table 7: Pulse and Blood Pressure Grading for Subjects 18-64 years of age

Physiologic Parameter	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Bradycardia - beats per minute	45 – 46	40 – 44	<40
Tachycardia - beats per minute	101 – 130	131 – 155	>155
Hypotension (systolic) mmHg	80 – 84	75 – 79	<75
Hypotension (diastolic) mmHg	50 – 54	45 – 49	<45
Hypertension (systolic) mmHg	151 – 155	156 – 160	>160
Hypertension (diastolic) mmHg	96 – 100	101 – 105	>105

[#] Pulse and blood pressure assessed on Day 1 prior to the first study vaccination will be considered as baseline.

8.1.3 Serious Adverse Events

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

- Death,
- A life-threatening AE*,
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- 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.

* Life-threatening AE. An AE is considered "life-threatening" if, in the view of either the site principal investigator 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.
- Recorded on the appropriate SAE data collection form and eCRF.
- Followed through resolution.
- Reviewed and evaluated by an Independent Safety Monitor (ISM) (as deemed necessary), the SMC (periodic review unless related), DMID, and the IRB.

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

8.2 Specifications of Safety Parameters

Safety will be assessed by the frequency and severity of:

8.2.1 Solicited Events

Solicited events are AEs that are common and known to occur following administration of study product.

8.2.2 Unsolicited Events

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

8.2.3 New Onset Chronic Medical Conditions (NOCMCs)

NOCMCs are defined as any new ICD-10 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.

8.2.4 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 emergency room 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.

8.2.5 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 B. LIST OF POTENTIALLY IMMUNE MEDIATED MEDICAL CONDITIONS

8.3 Reporting Procedures

Solicited injection site and systemic reactogenicity events will be documented and reported from the time of each study vaccination through 7 days after each study vaccination.

Clinical safety laboratory AEs will be documented and reported from the time of each study vaccination through approximately 7 days after each study vaccination.

Unsolicited non-serious AEs will be documented and reported from the time of each study vaccination through approximately 21 days after each study vaccination.

SAEs, MAAEs, including NOCMCs, and PIMMCs will be documented and reported from the time of the first study vaccination through approximately 12 months after the last study vaccination.

8.3.1 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)
6500 Rock Spring Dr. Suite 650
Bethesda, MD 20817, USA

[redacted]

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

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

The site will send a copy of the SAE report(s) to the ISM (as deemed necessary) when they are provided to the DMID Pharmacovigilance Group. 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 this trial, 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.

8.3.2 Regulatory Reporting for Studies Conducted Under DMID Sponsored IND

Following notification from the investigator, DMID, the Investigational New Drug (IND) sponsor, will report any suspected adverse reaction that is both serious and unexpected. DMID will report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the AE. DMID will notify FDA and all participating site investigators (i.e., all investigators to whom the sponsor is providing drug under its IND(s) or under any PI's IND(s)) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting as specified in 21 CFR Part 312.32. DMID will also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. 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 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 serious events designated as "not related" to study product(s), will be reported to the FDA at least annually in a summary format.

8.3.3 Reporting of Pregnancy

Pregnancies occurring in study subjects will be reported via AdvantageEDC^{SM} on the Pregnancy Report form. No further study vaccinations will be administered to pregnant subjects, but with the subject's permission all protocol-required venous blood samples will be obtained and the subject will continue to be followed for safety for the duration of this trial. Efforts will be made to follow all pregnancies reported during the course of this trial to pregnancy outcome pending the subject's permission.

8.3.4 Disclosure of Study Related Information

Subjects can choose to receive written disclosure of their treatment assignment after the database has been locked.

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

AEs will be collected, assessed, and followed through resolution from the time of each study vaccination through approximately 21 days after each study vaccination.

SAEs, MAAEs, including NOCMCs, and PIMMCs will be collected, assessed, and followed from the time of the first study vaccination through resolution even if this extends beyond the trial-reporting period (approximately 12 months after the last study vaccination).

Resolution of an AE/SAE is defined as the return to pretreatment status or stabilization of the condition with the expectation that it will remain chronic.

Follow-up procedures, evaluations, and outcomes will be recorded on the appropriate data collection form.

8.5 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, using a local laboratory as necessary. In determining eligibility, refer to section 5.1 and the protocol-specific MOP.

Clinical safety laboratory results[#] will be graded as follows:

Clinical Safety Laboratory Adverse Event Grading[#]

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
WBC 10^3/µL (Decrease)	2.5 – 3.9	1.5 – 2.4	<1.5
WBC 10^3/µL (Increase)	10.6 – 15.0	15.1 – 20.0	>20.0
Hgb g/dL (Decrease) (Female)	10.1 – 11.4	8.5 – 10	<8.5
Hgb g/dL (Decrease) (Male)	11.0 – 12.4	9.5 – 10.9	<9.5
Platelets 10^3/µL (Decrease)	125 – 139	100 – 124	<100
Platelets 10^3/µL (Increase)	416 – 550	551– 750	>750

Chemistry	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
ALT IU/L (Increase) (Female)	44 – 100	101 – 200	>200
ALT IU/L (Increase) (Male)	61 – 138	139 – 275	>275
Total Bilirubin mg/dL (Increase) – when accompanied by any increase in ALT	1.30 – 1.59	1.60 – 1.80	>1.80

Total Bilirubin mg/dL (Increase) – when ALT is normal	1.30 – 1.89	1.90 – 2.40	>2.40
Creatinine mg/dL (Increase) (Female)	1.1 – 1.7	1.8 – 2.0	>2.0
Creatinine mg/dL (Increase) (Male)	1.4 – 1.7	1.8 – 2.0	>2.0

[#] Clinical laboratory evaluations assessed on Day 1 prior to the first study vaccination will be considered as baseline.

8.6 Halting Rules

8.6.1 Study Halting Criteria

Further enrollment and study vaccinations will be halted for DSMB review/recommendation if any of the following are reported:

- Any subject experiences ulceration, abscess, or necrosis at the injection site related to study product administration.
- Any 2 or more subjects experience laryngospasm, bronchospasm, or anaphylaxis within 1 day after administration of study product that is considered related to study product.
- Three or more subjects experience generalized urticaria (defined as occurring at more than two body parts) within 3 days after administration of study product that is considered related to study product.
- Any subject experiences a study vaccine-related SAE from the time of the first study vaccination through the subject's last study visit.
- Any subject experiences acute weakness of limbs and/or cranial nerve innervated muscles (description of potential signal of GBS) after administration of study product.
- Any subject develops a PIMMC after administration of study product.

This trial will also be halted for DSMB review/recommendation if, within 7 days after administration of either study vaccination, any of the following occurs within the MF59®-adjuvanted treatment arms or within the one unadjuvanted treatment arm.

- 7% or more of subjects (with a minimum of 3 subjects) who received at least one dose of study vaccine to date, cumulative to both vaccine administrations, across all groups, experience the same severe (Grade 3) study vaccine-related injection site reaction.

Ecchymosis, erythema, and induration/swelling will also be measured in mm but size will not be used as halting criteria.

- 7% or more of subjects (with a minimum of 3 subjects) who received at least one dose of study vaccine to date, cumulative to both vaccine administrations, across all groups, experience the same severe (Grade 3) study vaccine-related subjective systemic reaction, for which the severity (grade) is corroborated by study personnel.

- 7% or more of subjects (with a minimum of 3 subjects) who received at least one dose of study vaccine to date, cumulative to both vaccine administrations, across all groups, experience the same severe (Grade 3) study vaccine-related quantitative systemic reaction.

- 7% or more of subjects (with a minimum of 3 subjects) who received at least one dose of study vaccine to date, cumulative to both vaccine administrations, across all groups, experience the same severe (Grade 3) study vaccine-related clinical safety laboratory AE.

Grading scales for solicited injection site and systemic (subjective and quantitative) reactions are included in Section 8.1.2.

Grading scales for clinical safety laboratory AEs are included in Section 8.5.

If any of the halting rules are met following any subject receipt of any study vaccination, then this trial will not continue with the remaining enrollments or study vaccinations without a review by and recommendation from the DSMB to proceed.

DMID retains the authority to suspend additional enrollment and study interventions/ administration of study product during the entire trial, as applicable.

The DMID Medical Monitor is empowered to stop enrollment and study vaccinations if AEs that meet the halting criteria are reported.

8.6.2 Individual Halting Criteria

The second study vaccination will not be administered to a subject if any of the following criteria are met:

- Subject meets any criteria in Section 5.2.1, Withdrawal from the Study or Discontinuation of the Study Product.

- Presence of signs or symptoms that could confound or confuse assessment of study vaccine reactogenicity. For subjects with injection site or systemic signs or symptoms, or with an acute illness, including an oral temperature greater than or equal to 100°F, the second study

vaccination should be postponed/deferred until signs, symptoms, or acute illness have resolved, or are improving as further specified below, and if within the acceptable protocol-specified window for that visit (Day 22+7) (note: Grade 1 vaccine related solicited AE are permitted, see below). No exceptions to the protocol-specified window will be made. **Note for afebrile, acute illness only:** If a subject is afebrile, his/her acute illness is nearly resolved with only minor residual symptoms remaining, this occurs within the acceptable protocol-specified window for that visit (Day 22+7), and, 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, the subject may receive the second study vaccination without further approval from the DMID Medical Officer. No exceptions to the protocol-specified window will be made.

- Grade 3 solicited or unsolicited AE that is ongoing, whether or not it is improved or resolving.

- Any unresolved or continuing Grade 2 AE that has not decreased in severity to Grade 1 or less.

- An unresolved or continuing Grade 1 AE is permissible following the documented determination by the site PI or appropriate sub-investigator, that it would not render study vaccination unsafe or interfere with the evaluation of responses.

- Grade 3 solicited or unsolicited AE that occurs without alternative etiology in the 8 days following the first study vaccination.

- Grade 3 clinical safety laboratory value (according to the toxicity table, Section 8.5) that does not decrease to Grade 2 or less prior to the second study vaccination. Any clinical safety laboratory parameter may be re-evaluated only once at the central (clinical) laboratory in order to assess eligibility prior to the second study vaccination. If the clinical safety laboratory value decreases to Grade 2 or less, the subject may receive the second study vaccination. The second study vaccination should be scheduled to occur within the acceptable protocol-specific window for that visit (Day 22+7 days post first study vaccination). No exceptions to the protocol-specified window will be made.

- Subject no longer meets eligibility criteria the Subject Exclusion Criteria (see Section 5.1.2). Note: exception for Medication changes described in Section 5.2.1.

- Hospitalization that occurs before administration of the second study vaccination.

8.7 Safety Oversight

8.7.1 Independent Safety Monitor (ISM)

The ISM is a physician with relevant expertise whose primary responsibility is to provide to DMID an independent safety assessment in a timely fashion. For this trial an ISM is not required. However, at each participating VTEU site, upon DMID Medical Monitor request, the PI will identify a physician with relevant expertise, to act as a Secondary Medical Assessor (SMA). The SMA will examine a subject and/or medical records and provide a medical assessment (or second medical opinion) to the DMID of the safety event in question. The PI will send to the DMID, MM, a summary of the event and include the PI and SMA assessments.

Note: In case that DMID has requested this type of evaluation multiple times, DMID may request the site(s) identify an ISM to assist DMID with safety oversight.

8.7.2 Data and Safety Monitoring Board (DSMB)

Safety oversight will be conducted by a DSMB that is an independent group of experts that monitors subject safety and advises DMID. The DSMB members will be separate and independent of study personnel participating in this trial and should not have scientific, financial or other conflict of interest related to this trial. The DSMB will consist of members with appropriate expertise to contribute to the interpretation of the data from this trial. The DSMB will operate under the rules of a DMID-approved charter that will be written at the organizational meeting of the DSMB. Procedures for DSMB reviews/meetings will be defined in the charter. Reports may include enrollment and demographic information, medical history, concomitant medications, physical assessments, clinical laboratory values, dosing compliance, and solicited and unsolicited AE/SAEs, HAI and Neut antibody assay results. The DSMB will review SAEs on a regular basis and ad hoc during this trial. The DMID Medical Monitor and the ISM (as deemed necessary) will be responsible for reviewing SAEs in real time.

The DSMB will conduct the following reviews:

- Bi-monthly (every two months) safety data reviews (including monthly safety data and cumulative safety data) until the last subject completes the visit that occurs approximately 21 days after the last study vaccination.

- Data review 9 days after all subjects have received Dose 2 (complete study visit number V06). This review may be conducted as part of the scheduled monthly reviews.

- Ad hoc when a halting rule is met or DMID/DSMB chair may convene an ad hoc meeting if there are immediate concerns regarding observations during the course of this trial.

- Final review meeting: 6 to 8 months after clinical database lock to review the cumulative unblinded safety and immunogenicity data for this trial. The data will be provided in a standard summary format. The DSMB may be asked to provide recommendations in response to questions posed by DMID.

Additional data may be requested by the DSMB, and interim statistical reports may be generated as deemed necessary and appropriate by DMID. The DSMB may receive data in aggregate and presented by treatment arm. The DSMB may also be provided with expected and observed rates of the expected AEs in an unblinded fashion, and may request the treatment assignment be unblinded for an individual subject if required for safety assessment. The DSMB will review grouped and unblinded data in the closed session only. As an outcome of each review/meeting, the DSMB will make a recommendation as to the advisability of proceeding with study vaccinations (as applicable), and to continue, modify, or terminate this trial.

9 HUMAN SUBJECT PROTECTION

9.1 Institutional Review Board/Independent Ethics Committee

Each 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 the Office of Human Research Protection (OHRP) as applicable to the research. DMID must receive the documentation that verifies IRB/IEC-approval for this protocol, associated ICFs, and upon request any recruitment material and handouts or surveys intended for the subjects, prior to 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. 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 Federal Wide Assurance (FWA) issued by the OHRP for federally funded research.

9.2 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 from the subject and documented. Subjects will receive a concise and focused presentation of key information about the clinical trial, verbally and with a written ICF. 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 have the opportunity to 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 principal investigator to subjects who consent to participate in this trial in accordance with IRB requirements. The ICF will be updated and subjects will be re-consented per IRB requirements, if necessary. Subjects will be given a copy of all ICFs that they sign.

9.3 Consent for Future Use of Stored Specimens and Data

Residual samples/specimens are those that are left over after protocol-specified testing and this study has been completed. Subjects may be asked for permission to keep any remaining (residual) serum derived from venous blood samples for possible use in future research studies, such as examining additional immunological assessments or testing for antibodies against other viruses or bacteria, or this permission may be a condition of study participation. Residual clinical samples for future use will be stored indefinitely at a central clinical storage facility and may be shared with investigators at the participating site and with other investigators at other institutions. The recipients of specimens will be informed that these specimens have a NIH certificate of confidentiality. The information provided to the recipient will not contain direct identifiable information. Use of the specimens will require review by an IRB.

Non-protocol Extra Samples

Other blood samples are being collected during the study specifically for future use, from subjects who consent to collection of those specimens either by signing an informed consent form that includes collection of future use samples as a condition of study participation or by indicating that they opt in to sample collection for future use if the informed consent allows the option to choose that option. It is anticipated that up to 5 mL of serum from venous blood samples will be available specifically for the purpose of future research, including but not limited to non-traditional immune assay development, assessing innate immune factors and the ability of H7 vaccine-induced antibodies to cross-react with other influenza viruses. These future use clinical samples will be stored indefinitely at a central clinical storage facility.

Residual specimens will be available upon the completion of this trial. Extra samples/specimens collected during this study may be requested from DMID CMS while this study is ongoing or after the study, after IRB review.

There are no benefits to subjects in the collection, storage and subsequent future use of their samples/specimens. Future use samples/specimens will not be sold or used directly for production of any commercial product. No genetic tests will be performed on samples/specimens. Each sample/specimen will be encoded (labeled) only with a barcode and a unique tracking number that connects to a code key at the study site. Restricted access to the code key is maintained by the PI to protect subject confidentiality. Reports from future research studies performed using subjects' samples/specimens will NOT be kept in their health records.

Subjects may be given the option to decide if they want their residual specimens to be used for future research or have these specimens destroyed at the end of this trial, or this permission may be a condition of study participation. If given the option, the subject's decision can be changed at any time by notifying the study doctors or nurses in writing. However, if the subject originally consents to the future use of residual specimens and subsequently changes his/her decision, any data from a previously collected specimen may be used for future research.

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

This trial will be inclusive of all subjects age 18 years and above who meet the Subject Inclusion Criteria (see Section 5.1.1) and do not meet the Subject Exclusion Criteria (see Section 5.1.2), regardless of religion, sex, or ethnic background. Should the outcome of this trial be deemed acceptable, additional trials may be initiated, including those in other populations.

It is unknown if the 2017 H7N9 IIV with or without MF59® adjuvant poses any risks to an unborn child. The available data for women who become pregnant during clinical trials of MF59®-adjuvanted (pre) pandemic influenza vaccines do not suggest any causal relationship between adverse pregnancy outcomes and receipt of an MF59®-adjuvanted vaccine. Women of childbearing age who have undergone sterilization via tubal sterilization, bilateral oophorectomy, salpingectomy, hysterectomy, or successful Essure® placement (permanent, non-surgical, non-hormonal sterilization) with documented radiological confirmation at least 90 days after the procedure are considered sterilized. All other women of childbearing age who are still menstruating or < 1 year out from the last menses if menopausal must agree to practice highly effective contraception that may include, but not limited to, 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, male or female condoms with spermicide or with the use of applied spermicide, intrauterine devices, NuvaRing®, and licensed hormonal methods such as implants, injectables, or oral contraceptives ("the pill"), with use of a highly effective method of

contraception for a minimum of 30 days prior to study product exposure and agree to practice highly effective contraception for the duration of study product exposure, including 60 days after their last study vaccination. A highly effective method of contraception is defined as one that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly. In addition to contraceptive use, all women of childbearing potential will be required to have a negative urine or serum pregnancy test within 24 hours prior to each study vaccination. If a female subject becomes pregnant while participating in this trial, we will ask her permission to follow-up with her about her health and the health of her baby through pregnancy outcome.

Children will not be included in this trial as presently there are no safety or efficacy data in adults.

9.5 Subject Confidentiality

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality includes documentation, investigation data, subject's clinical information, and all other information generated during participation in the study.

No information concerning the study or the data generated from the study will be released to any unauthorized third party without prior written approval of the DMID and the subject. Subject confidentiality will be maintained when study results are published or discussed in conferences.

The study monitor or other authorized representatives of the sponsor or governmental regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records. All records will be kept locked and all computer entry and networking programs will be carried out with coded numbers only and with password protected systems. All non-clinical specimens, evaluation forms, reports, and other records that leave the site will be identified only by a coded number.

9.6 Certificate of Confidentiality

To protect privacy we have 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, for example, if there is a court subpoena. 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 Food and Drug Administration (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.

9.7 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.

For this protocol, the study products (monovalent inactivated influenza 2017 H7N9 virus vaccine manufactured by Seqirus and adjuvant (MF59®) manufactured by Seqirus), are covered under the Public Readiness and Emergency Preparedness Act (PREP Act), as described in Section 2.1.1.

10 STATISTICAL CONSIDERATIONS

10.1 Study Hypotheses

This Phase II study is not designed to test a formal null hypothesis. Rather, it is intended to obtain sufficient data to obtain meaningful estimates of the immune response induced by this vaccine and to uncover any safety issues that occur at a sufficiently high rate that they might be observed in a study of this size. The sample size facilitates formal testing of selected hypotheses as discussed in Section 10.2, along with the probability of observing safety outcomes and the precision of immunogenicity outcomes.

10.2 Sample Size Considerations

This study is planned to enroll 106 subjects in each adjuvanted treatment arm, and 53 subjects in the unadjuvanted treatment arm. Randomization at each site will be stratified by prior receipt of seasonal influenza vaccines, however there is no enrollment target for these strata. The sample size for this study was selected to obtain preliminary estimates in a time critical manner. While this study is not designed to test any specific null hypothesis, the following tables illustrate the precision and power that is available for select estimates and comparisons of interest.

Table 8 indicates the probability of observing one or more safety events, such as solicited injection site or systemic reactogenicity events or an unsolicited non-serious AE of a particular type for a single treatment arm (N = 53, 106), and for all subjects receiving adjuvanted vaccine (N = 318).

Table 8: Power (%) to Detect Safety Events:

Event Frequency	N = 53	N = 106	N = 318
≥10% Very Common	>99	>99	>99
≥1% Common	41	65	95
≥0.1% Uncommon	45	10	27
≥0.01% Rare	<1	1	3

Binomial confidence intervals (CI) are widest (have the least precision) when the response rate is 50%.

is presented to indicate the worst case scenario for precision of observed exact (Clopper-Pearson) binomial confidence intervals.

Table 9: Precision of Binomial Confidence Intervals:

N	95% CI
53	36-64
106	40-60
318	44-56

Table 10 illustrates the minimum detectable differences in the proportion of subjects responding (e.g., attaining seroconversion or a titer ≥40) between two adjuvanted treatment arms using a two-sided Likelihood Ratio Test and alpha = 0.05.

Power calculations will assume n=100 per adjuvanted group and n=50 for the unadjuvanted group. Based on previous DMID A/H7N9 trials it is expected 5% of enrolled subjects may be excluded from analysis of the primary endpoint.

Table 10: Minimum Detectable Difference in Proportion Responders with 80% Power

Assumed Proportion of subjects with titer ≥40 in comparator arm	Minimum Detectable Difference (N = 100)
0.40	0.20
0.50	0.20
0.60	0.19
0.70	0.17
0.80	0.14
0.90	0.09

Per FDA guidance [67], the lower confidence limit on the appropriate point estimate excluding equality (i.e., a difference [adjuvanted – unadjuvanted] greater than zero in HAI antibody response rates) may be sufficient to demonstrate the added value of the adjuvant. Table 11 shows the lower bound of the 95% confidence interval for the differenc42 in the proportion responders between the adjuvanted and unadjuvanted arms (e.g. 15 mcg + MF59® minus 15 mcg unadjuvanted) assuming the proportion of responders in the unadjuvanted arm is 0.10 and considering a range for the proportion of responders in the adjuvanted arm ranges from 0.50 to 0.90.

Table 11: Lower Confidence bound2 for difference in proportion of responders between adjuvanted (N = 100) and unadjuvanted (N = 50) arms, 18-64 years stratum

Adjuvanted Arm	Unadjuvanted Arm	Difference	Lower Confidence Bound
0.50	0.10	0.40	0.26

0.60	0.10	0.50	0.36
0.70	0.10	0.60	0.46
0.80	0.10	0.70	0.56
0.90	0.10	0.80	0.67

10.3 Treatment Assignment Procedures

10.3.1 Randomization Procedures

Per ICH guideline E6: Good Clinical Practice (GCP), screening records will be kept at each participating 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 Statistical Data Coordinating Center's (SDCC) AdvantageEDC^{SM} (Electronic Data Capture System).

Once consented and upon entry of demographic data and confirmation of eligibility for this trial, the subject will be enrolled, randomly assigned to 1 of 4 treatment groups. All subjects will receive 2 vaccinations; the same dose will be given to the subject at both the first and second vaccination. Subjects will be randomized with allocation 2:2:2:1 into 4 groups, stratified by site (see Table 1) and by prior receipt of at least one of the 2017-2018 and/or 2018-2019 seasonal influenza vaccines to receive IM 2017 H7N9 IIV at 3.75 mcg, 7.5 mcg or 15 mcg at Days 1 and 22 with MF59® adjuvant or 15 mcg at Days 1 and 22 administered without adjuvant.

Enrollment of subjects will be done online using the enrollment module of AdvantageEDC^{SM}. The randomization code will be prepared by statisticians at the SDCC and included in the enrollment module for this trial. AdvantageEDC^{SM} will assign each subject to a treatment arm after the demographic and eligibility data have been entered into the system. A designated individual at each participating VTEU 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 AdvantageEDC^{SM} User's Guide. Manual back-up procedures and instructions are provided for use in the event that a participating VTEU site temporarily loses access to the Internet or the online enrollment system is unavailable.

10.3.2 Masking Procedures

This is a double-blind clinical trial.

Subjects, investigators, study personnel performing any study-related assessments following study vaccine administration are blinded to study treatment. Laboratory personnel performing HAI and Neut antibody assays will receive serum samples blinded to subject ID number and sample visit number.

The randomization scheme will be generated by the DCC and provided to unblinded study personnel (i.e., research pharmacists performing study vaccine preparations and unblinded study vaccine administrators) at the participating VTEU sites.

The unblinded study vaccine administrator is a study personnel member credentialed to administer vaccines and may also participate in dose preparation, but will not be involved in study-related assessments or have subject contact for data collection following study vaccine administration.

The Data and Safety Monitoring Board (DSMB) may receive data in aggregate and presented by treatment arm. The DSMB may also be provided with expected and observed rates of the expected AEs in an unblinded fashion, and may request the treatment arm be unblinded for an individual subject if required for safety assessment. The DSMB will review grouped and unblinded data in the closed session only.

10.4 Planned Interim Analyses

Interim analyses will only be used to terminate this trial in the event that unanticipated safety events deemed to be of sufficient concern require such action by the sponsor. These assessments will not be made on the basis of testing a formal statistical hypothesis; therefore, p-value adjustment will not be made to any analyses. A DSMB will be convened by DMID to review study progress and participant, clinical, safety, reactogenicity and immunogenicity data as described in Section 8.7.2.

A set of "topline" immunogenicity and safety tables produced on an expedited timeline will be prepared as described in section 10.6; though this report will be released while subjects remain in the trial for long-term safety follow-up, it will be considered the final analysis of these data. Emergent public health needs may dictate additional interim safety, reactogenicity, and/or immunogenicity analyses be performed on available information at any time during the trial. If this occurs, immunogenicity data will be analyzed as results are available from the central immunogenicity laboratory.

10.4.1 Interim Safety Review

An interim safety review may include enrollment and demographic information, medical history, concomitant medications, physical assessments, dosing compliance, and solicited and unsolicited AE/SAEs. Additional data may be requested by the DSMB, and interim statistical reports may be generated as deemed necessary and appropriate by DMID. The DSMB may receive data in aggregate and presented by treatment arm. The DSMB may also be provided with expected and observed rates of the expected AEs in an unblinded fashion, and may request the treatment assignment be unblinded for an individual subject if required for safety assessment. The DSMB

will review grouped and unblinded data in the closed session only. The DSMB will meet and review this data at scheduled time points or ad hoc as needed during this trial as defined in the DSMB charter. As an outcome of each review/meeting, the DSMB will make a recommendation as to the advisability of proceeding with study vaccinations (as applicable), and to continue, modify, or terminate this trial.

Additionally, this trial will be monitored to determine if any of the halting rules described in Section 8.6.1 are met.

10.4.2 Interim Immunogenicity or Efficacy Review

Should emergent public health needs dictate interim immunogenicity review, immune responses will be summarized in terms of strain-specific 2017 A/H7N9 HAI and Neut antibody titers**.** Any immunogenicity reports would be provided by the SDCC to the DMID Scientific Lead and CPM, and the DSMB. Reports would include data summarized by treatment arm.

10.5 Final Analysis Plan

Clinical, safety, and reactogenicity data through approximately 180 days after the second study vaccination will represent the primary clinical database for this trial. Once the last subject completes the visit that occurs approximately 180 days after second study vaccination and all HAI and Neut results are received, a "topline" subset of the immunogenicity and safety tables will be provided to DMID on an expedited timeline. These analyses may be made available to the sponsor for planning subsequent trials and to the lead PI for publication. These analyses will not be used to make any decisions concerning the conduct of this trial. As it is anticipated that subjects will remain in long term safety follow-up at the time of these analyses, blinded investigators and DMID medical monitors not involved in the analysis, publication, or clinical study report preparation will be responsible for assessing SAEs and MAAEs including PIMMCs and new onset chronic medical conditions until all subjects have completed the final follow-up visit. All analyses of data included in the topline tables for early release will be considered the final analysis of these data, and also included in the final clinical study report (CSR).

Analysis of exploratory immunogenicity endpoints may be performed and released as the data are available from the research laboratory. Any such analyses would be considered the final analysis for the endpoint, and included in the CSR. The final CSR will be completed after the last subject's last visit is completed, and the final clinical database including all long term safety follow-up data is cleaned, monitored and locked. Additional exploratory immunogenicity endpoint data not available at the time of CSR preparation may be included in an addendum to the CSR.

A formal statistical analysis plan will be developed and finalized prior to unblinding for any

analysis, which defines the analyses to be included in the topline tables and the final CSR.

10.5.1 Analysis Populations

The Safety Analysis population includes all subjects who received at least one dose of study vaccine.

The modified intent-to-treat (mITT) population includes all subjects who received at least one dose of study vaccine and contributed both pre- and at least one post-study vaccination venous blood samples for immunogenicity testing (HAI or Neut antibody assays) for which valid results were reported. For analyses using the mITT population, subjects will be grouped based on randomized treatment arm.

The per protocol (PP) population includes all subjects in the mITT subset with the following exclusions:

- Data from all available visits for subjects found to be ineligible at baseline.
- Data from all visits subsequent to major protocol deviations, such as:
  - Second study vaccination not received,
  - Second study vaccination received out of window,
  - Receipt of non-study licensed live vaccine within 30 days before or after each study vaccination,
  - Receipt of non-study licensed inactivated vaccine within 14 days before or after each study vaccination,
  - Receipt of immunosuppressive therapy (e.g., corticosteroids) within 30 days before or after each study vaccination.
  - Data from any visit that occurs substantially out of window.

For analyses using the PP population, subjects will be grouped based on study vaccinations received.

10.5.2 Safety Data

Summaries and analysis of safety data will be presented for the Safety Analysis Population. All summaries and analyses will be presented for all subjects.

Solicited AEs will be summarized by severity for each day after each study vaccination (Days 1-7 post each study vaccination) and as the maximum severity over all 8 days. Additionally, solicited AEs will be analyzed by taking the most severe response over the follow-up period,

dichotomizing into a binary variable (none versus mild, moderate, or severe) and using standard techniques, such as exact confidence intervals, to summarize the proportion of subjects reporting each symptom, any injection site symptom, and any systemic symptom. Summaries of solicited AEs will be presented separately for each study vaccination as well as overall study vaccinations by treatment arm. The proportion of subjects reporting symptoms may be compared between treatment arms using Chi-square or Fisher's exact test. The proportion of subjects reporting solicited symptoms between the different study vaccinations (i.e., first and second) will be compared using McNemar's test.

Unsolicited AEs will be coded by Medical Dictionary for Regulatory Activities (MedDRA®) for preferred term and system organ class (SOC). The numbers of SAEs, MAAEs, including 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 AEs), severity, relatedness, and outcome for each event. Non-serious unsolicited AEs will be summarized as number and percentage of subjects reporting at least one event in each MedDRA® preferred term and SOC, cross tabulated by severity and relationship to study product. Additionally, the proportion of subjects and exact 95% confidence intervals of AEs in aggregate and by MedDRA® categories will be computed.

10.5.3 Immunogenicity Data

Summaries and analysis of immunogenicity data will be presented for the mITT and PP populations.

Immune responses in terms of strain-specific 2017 H7N9 HAI and Neut antibody titers will be summarized by treatment arm at each time point. Analyses will include percentage of subjects with a titer ≥40, percentage of subjects achieving seroconversion (defined as either a pre-vaccination titer <10 and a post-vaccination titer ≥40 or a pre-vaccination titer ≥10 and a minimum four-fold rise in post-vaccination antibody titer), and GMTs along with corresponding 95% confidence intervals. Descriptive summary statistics will be provided for all assays and time points. The correlation between HAI and Neut antibody titers will be evaluated. Plots such as reverse cumulative distributions or longitudinal presentations of GMTs will be presented.

Additionally, the immune response, as described above, will be summarized by available covariates, such as age, sex, body mass index, and prior receipt of seasonal influenza vaccine(s), and these covariates may be considered statistical modeling. As an exploratory analysis, models will be developed to evaluate the relationship between dosage and adjuvant on immune response. For example, logistic regression may be used to examine the relationship of proportion of responders with dosage and adjuvant, and available covariates may be considered for inclusion in the model.

Additionally, N9 NA specific antibody assays are in development. N9 NA specific responses

may be assessed at baseline, and 8, 22, 29, 43 and 202 after receipt of the first study vaccination. For each time point summaries will include percentage of subjects with detectable N9 NA response (to be defined in SAP following assay development and selection) and GMTs along with corresponding 95% confidence intervals. Descriptive summary statistics will be provided for all assays and time points. The correlation of N9 NA response with HAI and Neut antibody titers will be evaluated, and plots such as reverse cumulative distributions or longitudinal presentations of GMTs will be presented.

Further, a determination of the NA content of the 2017 H7N9 IIV is planned if an assay becomes available and may be used to correlate the N9 NA elicited antibody responses to the NA content of the 2017 H7N9 IIV. Detectable NA antibody responses and GMTs will be summarized and evaluated for a dose response. If the NA content is available, NA antibody responses will be stratified by NA content, and statistical modeling may be used to examine the relationship of NA response with NA vaccine content, HA antigen dosage, and adjuvant.

At least a subset of samples will also be tested for cross-reactive serum HAI and Neut antibody responses to antigenically drifted variants of influenza A/H7 viruses. Strain-specific results will be summarized using descriptive statistics as described above, correlations with 2017 H7N9 responses, and association with study vaccine dose and adjuvant.

Further immunogenicity testing and/or analyses may be carried out in the future based upon subjects' prior receipt of non-seasonal influenza vaccines, including type (inactivated or live attenuated), what subtype (e.g. A/H3, A/H5, A/H9) and approximate date of vaccination.

10.5.4 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.

11 SOURCE DOCUMENTS ACCESS TO SOURCE DATA/DOCUMENTS

Each 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. Each site will permit authorized representatives of the DMID, its designees, and appropriate regulatory agencies to examine (and when required by applicable law, to copy) clinical trial records for the purposes of quality assurance reviews, audits, 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, subjects' Memory Aid or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

12 QUALITY CONTROL AND QUALITY ASSURANCE

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

The DCC 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(s) for clarification and resolution.

13 DATA HANDLING AND RECORD KEEPING

13.1 Data Management Responsibilities

The investigator is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported. All source data collection forms should be completed in a neat, legible manner to ensure accurate interpretation of data. Black or blue permanent ink is required to ensure clarity of reproduced copies. When making a change or correction, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source data collection forms and maintained for recording data for each subject enrolled in the study. Data reported in the eCRF derived from the source data collection forms should be consistent or the discrepancies should be explained.

The sponsor and/or its designee will provide guidance to the site PI and other study personnel on making corrections to the data collection forms and eCRF.

13.2 Data Coordinating Center/Biostatistician Responsibilities

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

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

13.3 Data Capture Methods

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

13.4 Types of Data

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

13.5 Study Records Retention

Study records and reports including, but not limited to, CRFs, source documents, ICFs, laboratory test results, and study drug disposition records will be retained for a minimum of 2 years after a marketing application is approved for the study product 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 future use will be maintained as long as the sample/specimen exists.

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

14 CLINICAL MONITORING

Site monitoring is conducted to ensure that the human subjects' protections, study and laboratory procedures, study intervention administration, and data collection processes are of high quality and meet sponsor, ICH/GCP guidelines and applicable regulations, and that this trial is conducted in accordance with the protocol, protocol-specific MOP and applicable sponsor standard operating procedures. 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 each participating site, study personnel, and all study documentation according to the DMID-approved site monitoring plan. Study monitors will meet with site PIs to discuss any problems and actions to be taken and document visit findings and discussions.

15 PUBLICATION POLICY

Following completion of the study, the lead 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 Statistical Analysis Plan will be posted on ClincialTrials.gov.

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

The responsible party plans not to request certification of delayed posting.

Refer to:

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

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17 APPENDICES

APPENDIX A: SCHEDULE OF PROCEDURES AND EVALUATIONS

APPENDIX B. LIST OF POTENTIALLY IMMUNE MEDIATED MEDICAL CONDITIONS

APPENDIX A: SCHEDULE OF PROCEDURES AND EVALUATIONS

Study Visit	**V00**	**V01**	**V02**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08**	**V09**	**V10**	**V11**	**Early Term**	**Unscheduled**
Study Day Post 1st Vaccination	**Screen Optional D-28 to -1**	**Dose 1 D1**	**D4 ±1d**	**D8 +2d**	**D22 +7d**	**D25**	**D29**	**D43**	**D82**	**D142**	**D202**	**D387**		
Study Day Post 2nd Vaccination					**Dose 2 D1**	**D4 ±1d**	**D8 +2d**	**D22 +7d**	**D61 ±7d**	**D121 ±14d**	**D181 ±14d**	**D366 ±14d**		
Obtain Informed Consent	X∞	X∞¬												
Collect Demographic Information	X	X†*												
Review Eligibility Criteria	X	X†¬			X†									
Medical History@	X	X†¬	X	X	X†	X	X	X			X		X	X(if indicated)
Concomitant Medications[5]	X	X†¬	X	X	X†	X	X	X	X	X	X		X (if within 180 days after last study vaccination)	X (if prior to 180 days after last study vaccination)
Vital Signs$ (Oral Temperature%, Pulse, and BP)	X	X†			X†2								X (may be obtained if indicated)	X (may be obtained if indicated)
Height and Weight	X	X†*												
Physical Examination[3]	X	X†*6		{X}	{X}†		{X}	{X}			{X}		{X}	{X}

Study Visit	**V00**	**V01**	**V02**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08**	**V09**	**V10**	**V11**	**Early Term**	**Unscheduled**
Study Day Post 1st Vaccination	**Screen Optional D-28 to -1**	**Dose 1 D1**	**D4 ±1d**	**D8 +2d**	**D22 +7d**	**D25**	**D29**	**D43**	**D82**	**D142**	**D202**	**D387**		
Study Day Post 2nd Vaccination					**Dose 2 D1**	**D4 ±1d**	**D8 +2d**	**D22 +7d**	**D61 ±7d**	**D121 ±14d**	**D181 ±14d**	**D366 ±14d**		
Serum or Urine Pregnancy Test	X^	X†^			X†^									
Venous Blood Collection for Clinical Safety Laboratory Evaluations		X[1]		X[1]	X[1]		X[1]						X (if within 7 days after the last study vaccination)	X (if indicated)
Venous Blood Collection for Immunongenicity Assays		X†		X	X†Ψ		X	X			XΨ		X (if within 21 days after last study vaccination)	X (if prior to 21 days after last study vaccination)
Serum Sample Collected for Future Research[4]		X†		X	X†		X	X			X		X(if within 21 days after last study vaccination	X(if prior to 21 days after last study vaccination
Enrollment in AdvantageEDC[SM] and Randomization		X†												
Pre-Administration Reactogenicity Assessments		X†			X†									
Study Vaccination		X			X									
20-minute Evaluation After Study Vaccination		X			X									
Examine Study Vaccination Site		X		X	X		X						X (if within 7 days after last study vaccination)	X (if within 7 days after last study vaccination)

Study Visit	**V00**	**V01**	**V02**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08**	**V09**	**V10**	**V11**	**Early Term**	**Unscheduled**
Study Day Post 1st Vaccination	**Screen Optional D-28 to -1**	**Dose 1 D1**	**D4 ±1d**	**D8 +2d**	**D22 +7d**	**D25**	**D29**	**D43**	**D82**	**D142**	**D202**	**D387**		
Study Day Post 2nd Vaccination					**Dose 2 D1**	**D4 ±1d**	**D8 +2d**	**D22 +7d**	**D61 ±7d**	**D121 ±14d**	**D181 ±14d**	**D366 ±14d**		
Post-Administration Reactogenicity Assessments		X			X								X (if within 7 days after last study vaccination)	X (if within 7 days after last study vaccination)
Distribute Memory Aid and Study-Related Materials		X			X									
Review Memory Aid			X	X		X	X						X (if within 7 days after last study vaccination)	X (if within 7 days after last study vaccination)
AE Assessment		X[&]	X[&]	X[&]	X[&]	X[&]	X[&]	X						X
SAEs/MAAEs/ NOCMCs/PIMMCs Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X
Phone Call			X			X			X	X		X		

∞ Prior to performing any study procedures.
† Prior to study vaccination.
Review results of safety laboratory evaluations¬ Review/confirm information or activity in subjects previously consented and screened
@ Complete medical history will be obtained by interview of subjects at the first visit (either screening [optional] or on Day 1 prior to the first study vaccination) and interim medical history will be obtained by interview of subjects at subsequent visits.
* Not required if done at the optional screening visit
$ Vital signs assessed on Day 1 prior to the first 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.
2 Vital signs are not required for subjects who are discontinued from receipt of the second study vaccination and are being followed for safety.
3 At the screening (or baseline if not done at screening) visit, a physical examination will be performed on all subjects to include the following organs and organ systems: skin, head and neck, lungs, heart, liver, spleen, extremities, lymph nodes, abdomen, general appearance, musculoskeletal, and nervous system and as assessment for signs suggestive of a PIMMC.
{}Targeted physical examination if indicated based on review of interim medical history.

^ Will be performed on all women of childbearing potential at screening (optional) and within 24 hours prior to each study vaccination and results must be negative and known prior to each study vaccination.

Ψ Subjects who do not receive the second study vaccination will continue with follow-up safety assessments (may be conducted by phone call) rather than in person continuing through approximately 12 months after their first study vaccination. These subjects will also be encouraged to provide a venous blood sample for anti-viral antibody assays at approximately 21 days after their first study vaccination

4 For subjects who have consented to collection of serum for future use either by signing an ICF that includes collection of future use samples as a condition of study participation or by indicating that they opt in to sample collection for future use if the ICF allows the option to choose that option.

& Inclusive of reactogenicity assessments performed on the day of each study vaccination through 7 days after each study vaccination.

5 All concomitant medications taken within 60 days prior to signing the ICF will be reviewed with subjects. Medications reported in the eCRF are limited to those taken within 30 days prior to the first study vaccination through approximately 180 days after the last study vaccination, including receipt of any non-study influenza vaccine.

6 Targeted physical examination may be done at Visit 01 if Visit 00, screening visit was conducted, and if indicated based on review of interim medical history.

APPENDIX B. LIST OF POTENTIALLY IMMUNE MEDIATED MEDICAL CONDITIONS

[also known as Adverse Events of Special Interest (AESIs). This list is not all inclusive].

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 rheumatica
- 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
- 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 (granulomatosis with polyangiitis), 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 IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis)
- Autoimmune myocarditis/cardiomyopathy
- Autoimmune thrombocytopenia
- Goodpasture syndrome
- Idiopathic pulmonary fibrosis
- Pernicious anemia
- Raynaud's phenomenon
- Sarcoidosis
- Sjögren's syndrome
- Stevens-Johnson syndrome
- Uveitis