A Phase II Study in Healthy Adults (19-64 Years of Age) to Assess the Safety, Reactogenicity and Immunogenicity of Sequential or Simultaneous Intramuscular Administration of an AS03-adjuvanted A/H7N9 Inactivated Influenza Vaccine with Seasonal Influenza Vaccine

DMID Protocol Number:

17-0077

DMID Funding Mechanism: Vaccine and Treatment Evaluation Units

Pharmaceutical Support:

Sanofi Pasteur
GlaxoSmithKline Biologicals

IND Sponsor: Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health

Lead Principal Investigator: Kathleen M. Neuzil, MD, MPH

DMID Clinical Project Manager: Tena Knudsen, RN

DMID Medical Monitor: Shy Shorer, MD, MBA, EJD

DMID Medical Officer: Trinka Coster, MD, MS

DMID Scientific Lead: Chris Roberts, PhD

Version: 5.0

September 18, 2018

STATEMENT OF COMPLIANCE

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

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

SIGNATURE PAGE

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

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

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

Site Principal Investigator:

Signed: _____ Date: _____

Name
Title

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

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/H5N3	Influenza A Virus of the H5N3 Subtype
A/H5N6	Influenza A Virus of the H5N6 Subtype
A/H7N7	Influenza A Virus of the H7N7 Subtype
A/H7N9	Influenza A Virus of the H7N9 Subtype
AS03	Adjuvant System 03
AdvantageEDC^{SM}	Electronic Data Capture System
AE	Adverse Event/Adverse Experience
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANCA	Anti-Neutrophil Cytoplasmic Antibody
BARDA	Biomedical Advanced Research and Development Authority
BLA	Biologics License Applications
BMI	Body Mass Index
BPM	Beats Per Minute
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CMS	Clinical Materials Services
Cr	Creatinine
CROMS	Clinical Research Operations and Management Support
CSL	Commonwealth Serum Laboratories
CSR	Clinical Study Report
°C	Degrees Celsius
°F	Degrees Fahrenheit
D	Day(s)
DCF	Data Collection Form
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
ESR	Erythrocyte Sedimentation Rate

FDA	Food and Drug Administration
FWA	Federalwide 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
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPAI	Highly Pathogenic Avian Influenza
HRSA	Health Resources and Services Administration
IATA	International Air Transport Association
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IgG	Immunoglobulin G
IIV	Inactivated Influenza 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)
mm	Millimeter(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, DHHS
NIH	National Institutes of Health
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
NOCMCs	New-Onset Chronic Medical Conditions
OER	Office of Extramural Research
OHRP	Office for Human Research Protections
PBS	Phosphate Buffered Saline
pH1N1	2009 H1N1 Influenza
PHI	Personal Health Information
PIMMCs	Potentially Immune-Mediated Medical Conditions
PLT	Platelets
PP	Per Protocol
PREP Act	Public Readiness and Emergency Preparedness Act
PRN	As Needed
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SAP	Statistical Analysis Plan
SDCC	Statistical and Data Coordinating Center
SOC	System Organ Class
SOP	Standard Operating Procedure
T. Bili	Total Bilirubin
TBD	To Be Determined
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 (19-64 Years of Age) to Assess the Safety, Reactogenicity and Immunogenicity of Sequential or Simultaneous Intramuscular Administration of an AS03-adjuvanted A/H7N9 Inactivated Influenza Vaccine with Seasonal Influenza Vaccine
Phase:	II
Population:	Approximately 150 individuals 19-64 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 4 Vaccine and Treatment Evaluation Unit (VTEU) sites
Study Duration:	Approximately sixteen (16) months
Subject Participation Duration:	Approximately thirteen (13) months
Estimated Time to Complete Enrollment:	Approximately 12 weeks
Description of Agent:	Two doses delivered intramuscularly (IM) approximately 21 days apart of an AS03-adjuvanted 2017 H7N9 inactivated influenza vaccine (IIV) (3.75 mcg hemagglutinin [HA] from A/Hong Kong/125/2017 H7N9 vaccine per dose) administered with a licensed seasonal influenza vaccine (15 mcg HA per strain per dose, quadrivalent IIV [IIV4]) given simultaneously with the first AS03-adjuvanted 2017 A/H7N9 IIV dose or sequentially at approximately 21 days prior to the first AS03-adjuvanted 2017 A/H7N9 IIV dose. One arm receiving only IIV4 is included as a comparator. All doses are to be given un-blinded following randomization.
Study Objectives:	**Primary:** Safety: • To assess the safety and reactogenicity following sequential or simultaneous IM administration of 2 doses of AS03-adjuvanted 2017 H7N9 IIV and one dose of seasonal influenza vaccine (IIV4). Immunogenicity:

- To assess the serum hemagglutination inhibition (HAI) and neutralizing (Neut) antibody responses against A/H7N9 at approximately 21 days following receipt of two doses of AS03-adjuvanted 2017 H7N9 IIV administered IM approximately 21 days apart.
- To assess the serum HAI and Neut antibody responses against the seasonal influenza strains at approximately 21 days following receipt of IIV4.

Secondary:

Safety:

- To assess unsolicited non-serious adverse events (AEs), following sequential or simultaneous IM administration of AS03-adjuvanted 2017 H7N9 IIV and seasonal influenza vaccine (IIV4).
- To assess medically-attended adverse events (MAAEs), including new-onset chronic medical conditions (NOCMCs) and potentially immune-mediated medical conditions (PIMMCs), following sequential or simultaneous IM administration of AS03 adjuvanted 2017 H7N9 IIV and IIV4.

Immunogenicity:

- To assess the HAI and Neut antibody responses at 21 days following receipt of 1 dose of AS03-adjuvanted 2017 H7N9 IIV.

Exploratory:

Immunogenicity:

- To assess the effects of age, sex, body mass index (BMI), and receipt of prior year(s) seasonal influenza vaccine(s) on serum HAI antibody responses following receipt of two doses of AS03-adjuvanted 2017 H7N9 IIV.
- To assess the durability of the antibody response to the 2017 H7N9 study vaccine strain and the IIV4 strains at approximately 180 days following the second dose of AS03-adjuvanted 2017 H7N9 IIV vaccine.
- To assess the neuraminidase (NA) content of the 2017 H7N9 IIV and the licensed seasonal IIV4 and determine the serum antibody responses to NA following receipt of 2017 H7N9 IIV and licensed seasonal IIV4.

Study Outcome Measures:

Primary:

Safety:

- Occurrence of all serious adverse events (SAEs) following the first study vaccination through approximately 12 months after the last study vaccination.
- Occurrence of study vaccine-related SAEs following the first study vaccination through approximately 12 months after the last study vaccination.
- Occurrence of solicited injection site and systemic AEs following each study vaccination through 7 days after each study vaccination.
- Occurrence of clinical safety laboratory AEs following each study vaccination through approximately 7 days after each study vaccination.

Immunogenicity:

- For HAI and Neut antibodies, percentage of subjects achieving seroconversion against the 2017 H7N9 study vaccine strain (defined as either a pre-vaccination titer <1:10 and a post-vaccination titer ≥1:40 or a pre-vaccination titer ≥1:10 and a minimum four-fold rise in post-vaccination antibody titer) at approximately 21 days after 2 doses of AS03-adjuvanted 2017 H7N9 IIV (Group 1– Day 43; Group 2 – Day 64; Group 3 – N/A).
- For HAI and Neut antibodies, percentage of subjects achieving seroconversion against each of the study IIV4 strains at approximately 21 days after receipt of study IIV4 (Groups 1, 2 and 3 – Day 22).
- For HAI and Neut antibodies, percentage of subjects with an antibody titer of ≥1:40 against the influenza 2017 H7N9 study vaccine strain at approximately 21 days following receipt of 2 doses of AS03-adjuvanted 2017 H7N9 IIV (Group 1– Day 43; Group 2 – Day 64; Group 3 – N/A).
- For HAI and Neut antibodies, percentage of subjects with an antibody titer of ≥1:40 against each of the study IIV4 strains at approximately 21 days after receipt of study IIV4 (Groups 1, 2 and 3 – Day 22).
- Geometric Mean Titers (GMTs) of serum HAI and Neut antibodies against the 2017 H7N9 IIV strain at approximately 21

days following receipt of 2 doses of AS03-adjuvanted 2017 H7N9 IIV (Group 1– Day 43; Group 2 – Day 64; Group 3 – N/A).

- GMTs of serum HAI and Neut antibodies against each of the 2017 IIV4 strains at approximately 21 days after receipt of IIV4 (Groups 1, 2, and 3 – Day 22).

Secondary:

Safety:

- Occurrence of study vaccine-related unsolicited non-serious AEs following each study vaccination through approximately 21 days after each study vaccination.
- Occurrence of all unsolicited non-serious AEs following each study vaccination through approximately 21 days after each study vaccination.
- Occurrence of MAAEs, including NOCMCs and PIMMCs, following 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 2017 H7N9 vaccine strain at approximately 21 days after receipt of 1 dose of AS03-adjuvanted 2017 H7N9 IIV (Group 1– Day 22; Group 2 – Day 43; Group 3 – N/A).
- For HAI and Neut antibodies, percentage of subjects achieving serum HAI and Neut antibody titers ≥1:40 against the influenza 2017 H7N9 vaccine strain at baseline and approximately 21 days after receipt of 1 dose of AS03-adjuvanted 2017 H7N9 IIV (Group 1–Day 1 (baseline) and Day 22; Group 2 –Day 22 (baseline), and Day 43; Group 3 – N/A).
- GMTs of serum HAI and Neut antibodies against the influenza 2017 H7N9 vaccine virus at baseline and at approximately 21 days after receipt of 1 dose of AS03-adjuvanted 2017 H7N9 IIV (Group 1–Day 1 (baseline) and Day 22; Group 2 –Day 22 (baseline), and Day 43; Group 3 – N/A).

Exploratory:

Immunogenicity: was manufactured using

- For HAI and Neut antibodies, percentage of subjects achieving seroconversion, percentage with titer ≥1:40 and the GMTs against the 2017 H7N9 study vaccine strain approximately 21 and 180 days after 2 doses of adjuvanted 2017 H7N9 IIV, stratified by age, sex, BMI, and prior receipt of seasonal influenza vaccine(s) for Groups 1 and 2.
- For HAI and Neut antibodies, percentage of subjects achieving seroconversion, percentage with a titer ≥1:40 and the GMTs against the IIV4 vaccine strains approximately 21 and 180 days after receipt of IIV4, stratified by age, sex, BMI, and prior receipt of seasonal influenza vaccine(s).
- For HAI and Neut antibodies, percentage of subjects achieving seroconversion, percentage with titer ≥1:40, and GMTs against the 2017 H7N9 study vaccine strain at approximately 180 days after 2 doses of adjuvanted 2017 H7N9 IIV for Groups 1 and 2.
- Percentage of subjects with detectable levels of serum N1, N2 and N9 NA-specific antibody elicited by 2017 H7N9 and seasonal IIV4 vaccination, and the correlation of the NA content of 2017 H7N9 IIV and seasonal IIV4 with the elicited NA-specific antibody responses at baseline and approximately 21 and 180 days after 2 doses of adjuvanted 2017 H7N9 IIV for Groups 1 and 2, and approximately 21 and 180 days after receipt of the seasonal IIV4 vaccine for all Groups.

Description of Study Design:

This is a randomized, un-blinded, Phase II study in males and non-pregnant females, who are in good health, 19 to 64 years of age. This clinical trial is designed to assess the safety, reactogenicity, and immunogenicity of a pre-pandemic AS03 (GlaxoSmithKline Biologicals [GSK]) adjuvanted 2017 monovalent inactivated influenza A/H7N9 vaccine (2017 H7N9 IIV) manufactured by Sanofi Pasteur (3.75 mcg of HA per dose), with Phosphate Buffered Saline (PBS) diluent, when two doses are administered 21 days apart either sequentially or simultaneously (within 15 minutes) with licensed seasonal influenza vaccine. [redacted]

IIV4 will be provided through the Division of Microbiology and Infectious Diseases (DMID) DMID Clinical Materials Services Contract (CMS), Fisher BioServices.

Subjects will be randomized into one of three treatment groups as shown in Table 1. Group 1 will receive two doses of AS03-adjuvanted 2017 H7N9 IIV, each dose administered IM approximately 21 days apart, and one dose of licensed seasonal IIV4 will be administered IM simultaneously (within 15 minutes) in opposite arms with the first dose of AS03 adjuvanted 2017 H7N9 IIV. Group 1 is the only Group, and only on study Day 1, that subjects will receive two vaccines administered IM simultaneously. Group 2 will receive one dose of IIV4 approximately 21 days prior to the IM administration of two doses of AS03-adjuvanted 2017 H7N9 IIV; each dose of AS03-adjuvanted 2017 H7N9 IIV will be given approximately 21 days apart. In Groups 1 and 2, the second dose of adjuvanted 2017 H7N9 IIV may be administered in the subject's preferred arm. If the subject has no preference, the second dose of adjuvanted 2017 H7N9 IIV may be given in either arm as long as there is no hindrance of the reactogenicity assessment. Group 3 will receive one dose IM of IIV4 as an un-blinded comparator in the subject's preferred arm.

Subjects who are in good health and meet all eligibility criteria (including an erythrocyte sedimentation rate [ESR], urine or serum pregnancy test, history and physical exam) within 28 days prior to the first vaccination or on the day of, but prior to, the first vaccination will be eligible for randomization as stated above. Baseline 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 and 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 collected for Group 1 on Days 1 (baseline), 22, and 43, and at approximately 180 days post second 2017 H7N9 IIV dose (Day 202), and for Group 2 on Days 22 (baseline), 43, and 64, and at approximately 180 days post second 2017 H7N9 IIV dose (Day 223). Serological antibody assays will

be performed against the vaccine viruses in IIV4 from serum samples collected at baseline (Day 1) and approximately 21 and 180 days following receipt of IIV4 (Groups 1, 2, and 3).

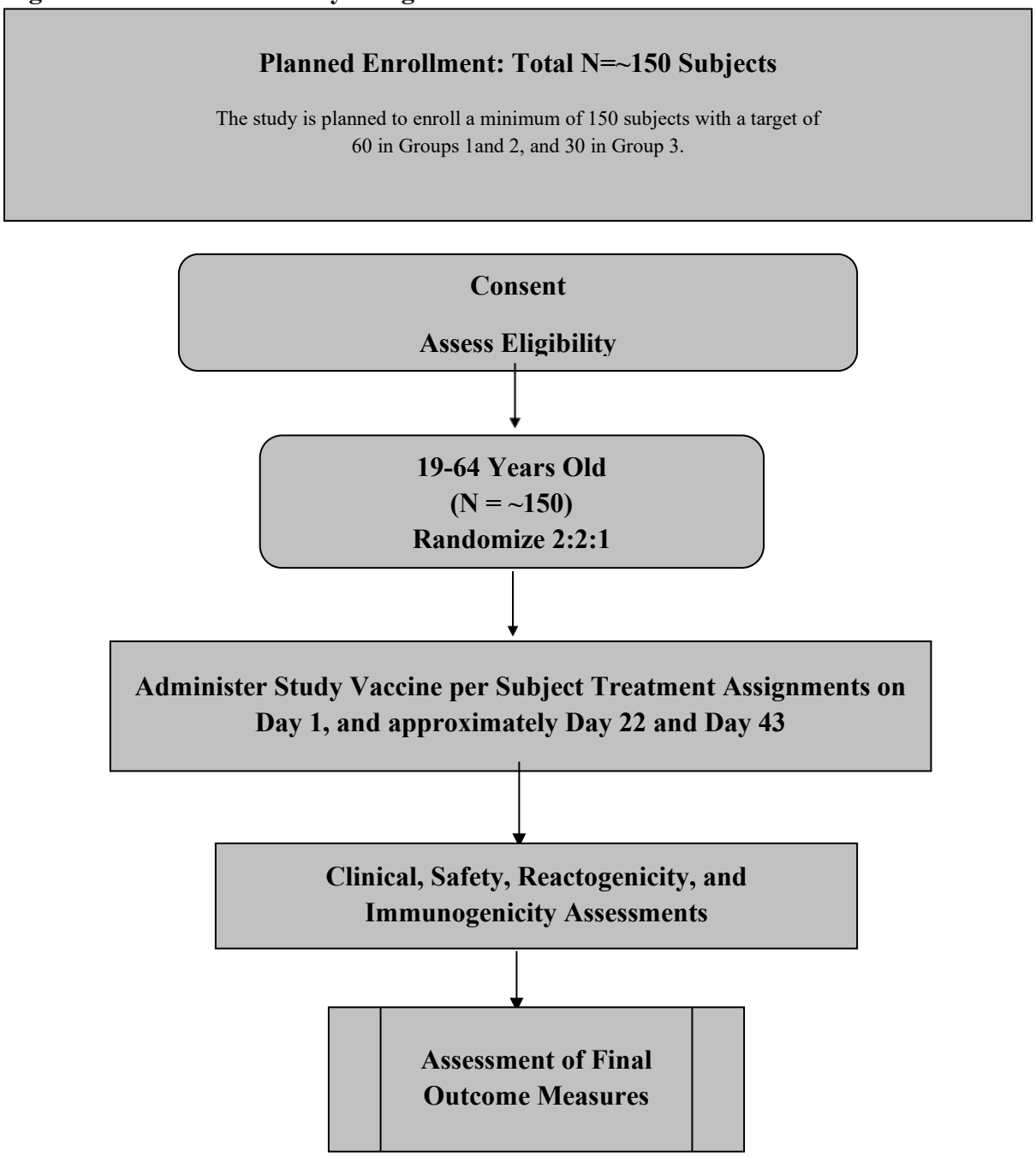
Novel methods for identifying and assessing alternative correlates of protection against influenza infection are needed. To assess the NA specific antibody response to vaccination, it is first necessary to determine the NA content of inactivated influenza vaccine; this assay is under development. If successful, the NA content in a dosage-specific manner can be correlated to the N9 NA-specific antibody responses elicited by the 2017 H7N9 IIV.

Subjects will be ineligible to participate in this trial if they have received the licensed 2017-2018 licensed seasonal IIV (IIV3 or IIV4, including high dose vaccine for the elderly) any time prior to enrollment; IIV4 will be provided at the first study vaccination to all participants in the study.

Table 1: Study Design

	Day 1 Dose 1	Approximately Day 22 Dose 2	Approximately Day 43 Dose 3
Group 1 (Age 19-64) n=60	Dose 1 (First and Second Study Vaccinations): Sanofi Pasteur H7N9 vaccine 3.75 mcg/ PBS diluent, plus GSK AS03 adjuvant + **IIV4**	Dose 2 (Third Study Vaccination): Sanofi Pasteur H7N9 vaccine 3.75 mcg/ PBS diluent, plus GSK AS03 adjuvant	N/A
Group 2 (Age 19-64) n=60	Dose 1 (First Study Vaccination): **IIV4**	Dose 2 (Second Study Vaccination): Sanofi Pasteur H7N9 vaccine 3.75 mcg/ PBS diluent, plus GSK AS03 adjuvant	Dose 3 (Third Study Vaccination): Sanofi Pasteur H7N9 vaccine 3.75 mcg/ PBS diluent, plus GSK AS03 adjuvant
Group 3 (Age 19-64) n=30	Dose 1 (First Study Vaccination): **IIV4**	N/A	N/A
Total Enrollment, n = ~150	Blood for HAI/Neut assays for 2017 H7N9 IIV will be collected: • for Group 1 on Days 1 (baseline), 22, and 43, and at approximately 180 days post second adjuvanted 2017 H7N9 IIV dose (Day 202) • for Group 2, on Days 22 (baseline), 43, and 64, and at approximately 180 days post second 2017 H7N9 IIV dose (Day 223). Serological antibody assays will also be performed against the vaccine viruses in IIV4 from serum samples collected at baseline (Day 1) and approximately 21 and 180 days following receipt of IIV4 (Groups 1, 2 and 3). Safety Lab Timepoints: Group 1: 4 timepoints per subject (Days 1, 8, 22, and 29) Group 2: 6 timepoints per subject (Days 1, 8, 22, 29, 43, and 50) Group 3: 2 timepoints per subject (Days 1 and 8) and Early Termination and /or Unscheduled Visits		

Figure 1: Schematic of Study Design



1 KEY ROLES

Lead Principal Investigator:	Kathleen M. Neuzil, MD, MPH Professor of Medicine and Pediatrics Director, Center for Vaccine Development University of Maryland School of Medicine
Co-Investigators:	Paul W. Spearman, MD (CCHMC) Cincinnati Children's Hospital Medical Center C. Buddy Creech, MD, MPH (Vanderbilt) Associate Professor of Pediatrics, Division of Pediatric Infectious Diseases Director, Vanderbilt Vaccine Research Program Paul Goepfert, MD (UAB) Professor of Medicine Director, Alabama Vaccine Research Clinic
DMID Clinical Project Manager:	Tena Knudsen, RN Division of Microbiology and Infectious Diseases NIAID, NIH 5601 Fishers Lane, Room 8E36, Bethesda, MD 20892-9825 Work: 240-627-3290 Email: knudsent@niaid.nih.gov
DMID Medical Monitor:	Shy Shorer, MD, MBA, RAC Division of Microbiology and Infectious Diseases NIAID, NIH 5601 Fishers Lane, Room 7E50 Rockville, MD 20892-9825 Phone: 240-627-3371 Email: shorers@niaid.nih.gov
DMID Medical Officer:	Trinka Coster, MD, MS Medical Officer, Respiratory Disease Branch Division of Microbiology and Infectious Diseases NIAID, NIH 5601 Fishers Lane, Room 8E25, MSC 9826

	Bethesda, MD 20852 Work: 301 538-2963 Email: trinka.coster@nih.gov
DMID Scientific Lead:	Chris Roberts, Ph.D. Division of Microbiology and Infectious Diseases NIAID/NIH/DHHS
Safety and Pharmacovigilance Contractor:	DMID Pharmacovigilance Group Clinical Research Operations and Management Support (CROMS) 6500 Rock Spring Dr., Suite 650 Bethesda, MD 20814 SAE Hot Line: 1-800-537-9979 (US) SAE Fax: 800-275-7619 (US) SAE Email: PVG@dmidcroms.com
Statistical and Data Coordinating Center:	The Emmes Corporation 401 N. Washington St., Suite 700 Rockville, MD 20850 Phone: 301-251-1161 Email: flutrials@emmes.com
Study Agent Repository:	Fisher BioServices c/o DMID Clinical Materials Services (CMS) Contract 20439 Seneca Meadows Parkway Germantown, MD 20876 Phone: 240-477-1350 Fax: 240-477-1360 Email: DMID.CMS@ThermoFisher.com
HAI and Neut Antibody Assays Laboratory:	Southern Research 2000 9th Avenue South Birmingham, AL 35205
NA Content Assays and NA Antibody Assays Laboratory:	TBD

2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

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 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 supports 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 inactivated seasonal influenza vaccines contain 7.5 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 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, and H7N9) 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 US, 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 GSK and Seqirus, respectively, has resulted in increased antibody responses to IIVs containing novel HAs in numerous clinical trials [29-33]. In an early study, dosage levels ranging from 3.75 to 30 mcg of A/H5N1 antigen administered with or without AS03 resulted in significant increases in antibody GMTs in groups who received the adjuvanted formulations [31]. These GMTs met the Committee for Medicinal Products for Human Use (CHMP) criterion for seroconversion rate (>40%) after a single dose with adjuvant. Following the second vaccine dose, all adjuvanted formulations complied with both CHMP and US Food and Drug Administration (FDA) criteria for seroconversion and seroprotection rates, whereas from the non-adjuvanted groups only the 30 mcg formulation met the CHMP criterion for seroconversion [31]. GSK received approval for the registration of a pre-pandemic AS03-adjuvanted, monovalent inactivated A/H5N1 virus vaccine by European regulatory authorities in 2008 and FDA approval of their Biologics License Applications (BLA) for Influenza A (H5N1) Virus Monovalent Vaccine Adjuvanted (with AS03) in 2013.

Following the 2009 emergence of the novel A/H1N1 pandemic virus, the European Commission granted marketing authorization of GSK's egg-derived AS03-adjuvanted monovalent inactivated 2009 A/H1N1 virus vaccine (Pandemrix™) and Novartis' egg-derived MF59-adjuvanted, monovalent inactivated 2009 A/H1N1 virus vaccine (FOCETRIA™). These adjuvanted

monovalent inactivated 2009 A/H1N1 virus vaccines were widely used throughout Europe and in many other countries, albeit not in the US.

The inclusion of adjuvants in clinical trials evaluating IIVs has also frequently been associated with increased injection site reactogenicity [26]. Additionally, in late 2010, a possible association between an increased risk of narcolepsy in children and adolescents who had received the AS03-containing Pandemrix™ was reported in Finland and Sweden. Some, but not all, countries in which retrospective studies were conducted showed a similar association [34-43]. (See also Section 2.3.1 Potential Risks for further discussion).

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 AS03 and MF59 adjuvants. The National Institute of Allergy and Infectious Diseases (NIAID) has conducted several clinical trials to evaluate 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 [44-49]. In response to emerging H5N8 viruses that have caused extensive outbreaks in domestic poultry and wild birds in South East Asia [50, 51], NIAID is also conducting 2 ongoing 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 [52], 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 December 7, 2017 a total of 1,565 laboratory-confirmed human infections with avian influenza A/H7N9 virus have been reported by the World Health Organization (WHO) [53, 54]. Whereas most cases have been centered in and around mainland China, there have been several traveler associated cases, including two in travelers reported by Canada who were returning from China in early 2015 [55]. 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 [53]. 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 [56, 57].

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 [54]. 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 [53, 58].

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 vaccine 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 Sanofi Pasteur and adjuvant (AS03) manufactured by GSK, 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 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

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 Novartis (now Seqirus), respectively. In general, these trials have demonstrated that adjuvant use results in a significant dose-sparing effect. NIAID is currently conducting similar "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 [54, 58]. 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.

The potential for a negative effect of prior seasonal vaccination on vaccine effectiveness and immunogenicity has been debated for decades [59, 60]. In recent years, several observational studies have reported that the response to and effectiveness of influenza vaccine during any given season may be modified by receipt of seasonal influenza vaccine in prior seasons [61-63]. Likewise, several evaluations of H5N1 and 2009 H1N1 vaccines suggest that prior receipt of seasonal vaccine is associated with a lower response to H5N1 or 2009 H1N1 vaccines, respectively [64-67]. Similar immunological interference has been reported in individuals who received seasonal IIV3 in the weeks to months prior to H1N1 and H5N1 vaccines, whereas other studies failed to identify significant differences or observed improved responses [67-69].

Overall, the effects of prior vaccination have not been observed consistently across all studies and seasons, and likely differ by timing of vaccine administration, influenza virus type or subtype, and presence and type of adjuvant used. In regards to H7N9 vaccines, as reported by Jackson et al., generally higher GMTs and proportion with an HAI titer of 40 or higher at 21 days after dose 2 were observed in the group that did not receive seasonal influenza vaccine. In a logistic regression model, older age and prior receipt of seasonal influenza vaccine were independently associated with a lower likelihood of achieving an HAI titer of 40 or higher after dose 2 [47]. In the Jackson et al. study, the receipt of seasonal vaccines occurred before the start of the trial, as reported by the participants. Data from randomized control trials of seasonal vaccines given concomitantly or sequentially with H7N9 vaccines are not available.

The goal of this clinical trial is to assess the safety, reactogenicity and immunogenicity of two doses of AS03-adjuvanted 2017 H7N9 IIV administered sequentially or simultaneous with seasonal influenza vaccine and to assess potential interference with the immunogenicity of either vaccine. The public health goal would be to maximize protection to the seasonal strains and H7N9 strain in the target population while ensuring acceptable tolerability and safety. While the prior seasonal influenza vaccine history of the target population will vary substantially and cannot be readily altered, it is important to understand the effects of simultaneous versus sequential delivery of H7N9 strains with currently available seasonal influenza vaccines to inform vaccination programs. This study will provide important information on two scenarios 1) seasonal influenza vaccine given with the first dose of H7N9 and 2) seasonal influenza vaccine given prior to H7N9 vaccine.

Another goal of this study is to assess, in at least a subset of samples, if serum IgG elicited by the 2017 H7N9 IIV recognize 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-specific correlation of NA content with elicited humoral antibody responses to the N9 NA.

Based on previously conducted studies with a 2013 H7N9 IIV manufactured by Sanofi Pasteur administered with AS03, we anticipate that two doses of the 2017 H7N9 IIV administered IM with AS03 adjuvant approximately 21 days apart will be well-tolerated.

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 monovalent inactivated influenza H7N9 vaccine plus PBS diluent and/or AS03 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 amount of risk to subjects who report that they are in good health but who have an unknown health problem at the time of screening. This trial will screen by physical exam, history, vital signs and sedimentation rate. Baseline safety labs for white blood cells (WBC), hemoglobin (Hgb), platelets (PLT), alanine aminotransferase (ALT), total bilirubin (T. Bili), and creatinine (Cr) will be drawn prior to study vaccination but results will not be reviewed until after study vaccination. To minimize the risk, subjects will not receive the second study vaccination unless, the most recently evaluated clinical safety laboratory values obtained prior to the second study vaccination are Grade 2 or less and the subject does not meet any of the other criteria listed in Section 5.2.3.

There is potential for AEs to occur more frequently in the adjuvanted vaccine groups [70] 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

monovalent A/H7N9 vaccine 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 sponsored two Phase II clinical trials that included an assessment of the safety, reactogenicity, and immunogenicity of two IM doses of a monovalent A/H7N9 vaccine produced by Sanofi Pasteur, Swiftwater, PA, administered with or without AS03 in healthy adults (DMID Protocol 13-0032; NCT01938742 and DMID Protocol 13-0033; NCT01942265).

Overall, the study products administered in both of 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 cases of Autoimmune thyroiditis (Hashimoto's disease/Hashimoto's thyroiditis) or Adverse Events of Special Interest (AESIs) were reported in this clinical trial: one case was assessed as not related to study product (due to preexisting Thyroid Peroxidase Antibodies) and the second case was assessed as related to study product (no preexisting Thyroid Peroxidase Antibodies).

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 current monovalent split IIV was derived from the influenza virus A/Hong Kong/125/2017 (H7N9). The manufacturing process for the production of this investigational A/H7N9 vaccine is similar to the process used to produce the licensed Influenza Virus Vaccine Fluzone® family of products. As such, the safety profile of the candidate A/H7N9 vaccine should be similar to the current Fluzone® vaccine. [redacted] formulation has been determined by [redacted] In this clinical trial, the labeling of the original [redacted] The vaccine preparation has been adjusted to meet the targeted concentration by [redacted] was produced in accordance with the commercial process [redacted] The final vaccine preparation is [redacted]

The potential risks to subjects are anticipated to be similar to those observed for Sanofi Pasteur's unadjuvanted licensed inter-pandemic (seasonal) IIVs (Fluzone® and Fluzone® High-Dose), their unadjuvanted licensed 2009 A/H1N1 and A/H5N1 monovalent IIVs, and for previously conducted 2013 H7N9 IIV administered with and without AS03 and MF59 (see the Sanofi

Pasteur Investigator's Brochure (Investigational Pandemic Influenza Virus vaccines, Monovalent A/Shanghai/2/2013 (H7N9) product code 504, Monovalent A/Hong Kong/125/2017 (H7N9) product code 504, Monovalent A/Indonesia/05/2005 (H5N1) product code 458, Monovalent A/Vietnam/1203/2004 (H5N1) product code 399, Monovalent A/Bar-Headed Goose/Qinghai Lake/1A/2005 (H5N1) product code 458, Version Number 1.0, January 2018).

Occasionally, adult recipients of unadjuvanted licensed, IIVs may develop influenza-like reactions, such as fever, feverishness (chills/shivering/sweating), fatigue (tiredness), malaise (general unwell feeling), myalgia (body aches/muscular pain), arthralgia (joint pain), headache, and/or nausea. Some subjects may develop reactions at the injection site, including pruritus (itching), ecchymosis (bruising), erythema (redness), induration (hardness), edema (swelling), pain, and/or tenderness. Most of these reactions peak in intensity in the first 24 hours after vaccination and disappear without treatment within 1 or 2 days. Analgesics (e.g., acetaminophen, ibuprofen, or similar non-steroidal anti-inflammatory drugs [NSAIDs]) and rest may generally relieve or lessen these reactions. Bruising can sometimes occur due to the vaccination procedure.

In addition, post-marketing surveillance indicates autoimmune disorders as potential risks for pandemic vaccines based on those identified for the seasonal IIVs; these may also include, but are not limited to, neuritis, convulsions, severe allergic reactions, syncope, encephalitis, thrombocytopenia, vasculitis, and Guillain-Barré syndrome (GBS). Reports of these reactions were rare; however, exact incidence rates cannot be precisely calculated.

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 vaccination. These reactions can manifest as skin rash (hives), swelling around the mouth, throat, or eyes (angioedema), difficulty breathing (bronchospasm), a fast pulse (tachycardia), or decrease in blood pressure (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 [71]. Interestingly, although vaccination rates have increased in the last 10 years, the numbers of reported cases of vaccine-associated GBS have declined [72]. 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 [73]. 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 [74-76]. Another study using the Medicare system showed an elevated risk of GBS with 2009 monovalent H1N1 vaccination (incidence rate ratio = 2.41, 95% confidence interval (CI): 1.14, 5.11; attributable risk = 2.84 per million doses administered, 95% CI: 0.21, 5.48) [77]. An international collaboration study also supported a conclusion of an association between 2009 H1N1 vaccination and GBS [78]. It is unknown if the administration of the monovalent inactivated influenza 2017 H7N9 virus vaccine 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.

As of November 22, 2015 (per the manufacturer's IB dated February 2016), data are available for 56 GSK sponsored clinical trials of AS03-adjuvanted monovalent pandemic vaccines manufactured by GSK. More than 18,000 adults (age ≥18 years) and 6,900 pediatric (6 months to 17 years old) clinical trial participants have received at least one dose of a GSK-manufactured, AS03-adjuvanted monovalent pandemic influenza vaccine. Clinical data collected by GSK as of November 22, 2015, suggest that inactivated monovalent (pre)pandemic influenza virus antigens adjuvanted with AS03 have generally acceptable safety and benefit/risk profiles, though the incidence rates of solicited local and systemic AEs are higher with AS03-adjuvanted antigens than with antigen alone, a licensed IIV3, or placebo. Some unsolicited AEs (e.g., insomnia, dizziness, cystitis) were associated with a higher relative risk among H5N1/AS03 recipients in contrast to Fluarix® or placebo recipients.

The information and guidance that follow are based on pre-clinical and clinical study results for GSK-manufactured AS03-adjuvanted monovalent pandemic vaccines, post-marketing safety surveillance data seen with unadjuvanted, IIV3s and (in the case of the H1N1 vaccines) post-marketing safety surveillance data seen to date for both Pandemrix™ and Arepanrix™ H1N1 vaccines.

The reactogenicity profile in humans of GSK-manufactured AS03-adjuvanted vaccines is primarily associated with the adjuvant. The incidence and severity of injection site redness, swelling, and pain at the injection site in recipients of AS03-adjuvanted vaccines are increased relative to monovalent pandemic influenza antigen alone, a licensed IIV3, or placebo. There is no increase in injection site and systemic reactogenicity events in recipients of AS03-adjuvanted vaccines after a second dose of vaccine relative to the first when given 21 days apart. In young

children (6 months to 6 years old), increased frequency of fever has been observed following a heterologous booster dose of adjuvanted vaccine administered 6 months after the primary series.

As of November 22, 2015, there has been no evidence in clinical trials to support a conclusion that any potential immune-mediated disease or group of diseases was causally related to an AS03-adjuvanted vaccine. There have been no deaths in GSK clinical trials of AS03-adjuvanted pandemic influenza vaccines assessed as related to study vaccine. A total of 1,428 non-fatal SAEs have been reported for adult subjects as of November 22, 2015. Fifteen of these events were deemed related to vaccination by the Investigator or GSK. Of these, six occurred in recipients of an adjuvanted H1N1 vaccine: asthma, herpes zoster, hepatic enzyme increased, and pain in extremity, polymyalgia rheumatic, and thrombocytopenia. Three occurred in recipients of unadjuvanted H1N1 vaccine: alanine aminotransferase increased, hypersensitivity, and multiple sclerosis. One SAE classified as related (myalgia) occurred in a subject who received a control product. Four SAEs classified as related occurred in recipients of an adjuvanted H5N1 vaccine: autoimmune hepatitis, angina pectoris, pulmonary embolism, and non-Hodgkin's lymphoma. One SAE classified as related (lobar pneumonia) occurred in a recipient of an unadjuvanted H5N1 vaccine. Overall, the reactogenicity and safety profile of AS03-adjuvanted pandemic vaccines is acceptable and no safety concerns have been identified in clinical trials.

Narcolepsy is a chronic sleep disorder with a background incidence rate, based on US data, of approximately 1.37 per 100,000 per year, with a peak onset between 10 and 19 years of age in some datasets. Narcolepsy, when associated with cataplexy is seen almost exclusively in individuals who are HLA DQB1*0602 allele carriers [79]. An autoimmune etiology has been proposed. In the post-marketing period for adjuvanted H1N1 pandemic vaccines, several epidemiological studies conducted in several countries independently of GSK reported an increased risk of narcolepsy with or without cataplexy in subjects who were vaccinated with Dresden-manufactured H1N1 (Pandemrix™ H1N1) vaccine during the 2009-2010 season. These studies have described an absolute risk increase of narcolepsy of approximately 1.4 to 8 additional cases per 100,000 vaccinated children/adolescents, and approximately one additional case per 100,000 vaccinated adults compared to background rates of 0.12 to 0.79 per 100,000 children/adolescents per year and 0.67 to 1.10 per 100,000 adults per year. The observed temporal association between narcolepsy and vaccination with Pandemrix™ H1N1 is not fully understood, and further research to evaluate the association between narcolepsy and Pandemrix™ H1N1, and other possible contributory factors to the development of narcolepsy during the 2009-2010 pandemic, such as genetic and environmental factors, is being conducted. A GSK-supported study was conducted in Quebec, Canada, to assess the risk of narcolepsy associated with Arepanrix H1N1, using various index dates, risk periods, observation periods, and epidemiological designs. Overall, GSK considers that there is no strong evidence of an association between Q-Pan-H1N1 and narcolepsy in Quebec. Recently, the CDC conducted a study to assess trends in narcolepsy incidence rates before and after 2009 H1N1 influenza

(pH1N1) vaccination campaigns and to evaluate the risk of narcolepsy following adjuvanted pH1N1 vaccines. Results of the incidence rates analysis indicated no change in narcolepsy rates between the period before wild-type pH1N1 virus circulation and the period after the start of pH1N1vaccination campaigns in any countries except Sweden, the first signaling country, and Taiwan, where incidence began to increase upon wild-type pH1N1 virus circulation. In the case-control analysis, no association was observed for AS03-adjuvanted pH1N1 vaccine and narcolepsy in children or adults, and in the case-coverage analysis, no association was observed for narcolepsy in children, the only age groups studied. However, the data for the AS03-adjuvanted pH1N1 vaccine, Pandemrix™, were limited. (20th Annual Conference on Vaccine Research, April 24-26th, 2017, Abstract S6-1).

No post-marketing data are available for AS03 administered in combination with any GSK-manufactured H5N1, H7N1, H7N9, or H9N2 antigen. However, millions of doses of GSK-manufactured H1N1 antigens, combined with AS03, were administered in the context of the 2009/10 pandemic response. In addition to the adverse reactions reported in clinical trials, the following have been reported during post-marketing experience with Pandemrix™ (H1N1) and Arepanrix™ (H1N1):

- Immune system disorders
    - Rare: anaphylaxis, allergic reactions
- Nervous system disorders
    - Rare: febrile convulsions (in subjects below 20 years of age), somnolence**, GBS*

      **Spontaneous reports of GBS syndrome have been received following vaccination with Arepanrix™ (H1N1); however, a causal association between vaccination and GBS has not been established. Data from a post-marketing epidemiological study in Canada indicate a small but significant increased relative risk of GBS of 1.80 (95% CI, 1.63-4.62) in the 56-day period following vaccination with Arepanrix™ (H1N1, in persons 50 years of age and older). The number of GBS cases attributable to vaccination was approximately 2 per 1 million doses.*

      ***reported in patients with narcolepsy and as a temporary event following vaccination*

    - Very rare[1]: narcolepsy with or without cataplexy

      [1]Frequency based on estimated attributable risk from epidemiological studies in several European countries.

- Skin and subcutaneous tissue disorders
    - Rare: angioedema, generalized skin reactions, urticaria
- General disorders and administration site conditions
    - Rare: injection site reactions (such as inflammation, mass, ecchymosis)

From post-marketing surveillance with interpandemic (seasonal) trivalent vaccines, the following additional AEs have been reported:

- Blood and lymphatic system disorders
    - Transient thrombocytopenia
- Nervous system disorders
    - Neuralgia, convulsions
    - Neurological disorders, such as encephalomyelitis, neuritis, and GBS
- Vascular disorders
    - Vasculitis with transient renal involvement

As of November 22, 2015, the available data for women who become pregnant during clinical trials of AS03-adjuvanted (pre) pandemic influenza vaccines do not suggest any causal relationship between adverse pregnancy outcomes and receipt of an AS03-adjuvanted vaccine. However, there is no available data related to the risks of exposure to H7N9 vaccines administered with or without AS03 upon pregnancy and pregnancy outcomes.

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 Known Potential Benefits

There are no known benefits attributable to the receipt of the 2017 H7N9 IIV in PBS with or without AS03 adjuvant. Vaccination using the 2017 H7N9 IIV with AS03 adjuvant may or may not provide protection against a serious disease with the influenza 2017 H7N9 virus, should the participant be exposed. The duration of any such protection is currently unknown. The 2017 H7N9 IIV with or without AS03 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 OBJECTIVES AND OUTCOME MEASURES

3.1 Study Objectives

3.1.1 Primary

Safety:

- To assess the safety and reactogenicity following sequential or simultaneous IM administration of 2 doses of AS03-adjuvanted 2017 H7N9 IIV and one dose of seasonal influenza vaccine (IIV4).

Immunogenicity:

- To assess the serum HAI and Neut antibody responses against A/H7N9 at approximately 21 days following receipt of two doses of AS03-adjuvanted 2017 H7N9 IIV administered IM approximately 21 days apart.
- To assess the serum HAI and Neut antibody responses against the seasonal influenza strains at approximately 21 days following receipt of IIV4.

3.1.2 Secondary

Safety:

- To assess unsolicited non-SAEs following sequential or simultaneous IM administration of AS03-adjuvanted 2017 H7N9 IIV and seasonal influenza vaccine (IIV4)
- To assess MAAEs, including NOCMCs and PIMMCs, following sequential or simultaneous IM administration of AS03-adjuvanted 2017 H7N9 IIV and IIV4

Immunogenicity:

- To assess the HAI and Neut antibody responses at 21 days following receipt of 1 dose of AS03-adjuvanted 2017 H7N9 IIV.

3.1.3 Exploratory

Immunogenicity:

- To assess the effects of age, sex, BMI, and receipt of prior year(s) seasonal influenza vaccine(s) on serum HAI antibody responses following receipt of two doses of AS03-adjuvanted 2017 H7N9 IIV.
- To assess the durability of the antibody response to the 2017 H7N9 study vaccine strain and the IIV4 strains at approximately 180 days following the second dose of AS03-adjuvanted 2017 H7N9 IIV vaccine.
- To assess the NA content of the 2017 H7N9 IIV and the licensed seasonal IIV4 and determine the serum antibody responses to NA following receipt of 2017 H7N9 IIV and licensed seasonal IIV4.

3.2 Study Outcome Measures

3.2.1 Primary

Safety:

- Occurrence of all SAEs following the first study vaccination through approximately 12 months after the last study vaccination.
- Occurrence of study vaccine-related SAEs following the first study vaccination through approximately 12 months after the last study vaccination.
- Occurrence of solicited injection site and systemic AEs following each study vaccination through 7 days after each study vaccination.
- Occurrence of clinical safety laboratory AEs following each study vaccination through approximately 7 days after each study vaccination.

Immunogenicity:

- For HAI and Neut antibodies, percentage of subjects achieving seroconversion against the 2017 H7N9 study vaccine strain (defined as either a pre-vaccination titer <1:10 and a post-vaccination titer ≥1:40 or a pre-vaccination titer ≥1:10 and a minimum four-fold rise in post-vaccination antibody titer) at approximately 21 days after 2 doses of AS03-adjuvanted 2017 H7N9 IIV (Group 1– Day 43; Group 2 – Day 64; Group 3 – N/A).
- For HAI and Neut antibodies, percentage of subjects achieving seroconversion against each of the study IIV4 strains at approximately 21 days after receipt of study IIV4 (Groups 1, 2 and 3 – Day 22).
- For HAI and Neut antibodies, percentage of subjects with an antibody titer of ≥1:40 against the influenza 2017 H7N9 study vaccine strain at approximately 21 days following

receipt of 2 doses of AS03-adjuvanted 2017 H7N9 IIV (Group 1 – Day 43; Groups 2 – Day 64; Group 3 – N/A).

- For HAI and Neut antibodies, percentage of subjects with an antibody titer of ≥1:40 against each of the study IIV4 strains at approximately 21 days after receipt of study IIV4 (Groups 1, 2 and 3 – Day 22).
- GMTs of serum HAI and Neut antibodies against the 2017 H7N9 IIV strain at approximately 21 days following receipt of 2 doses of AS03-adjuvanted 2017 H7N9 IIV (Group 1– Day 43; Group 2 – Day 64; Group 3 – N/A).
- GMTs of serum HAI and Neut antibodies against each of the 2017 IIV4 strains at approximately 21 days after receipt of IIV4 (Group 1, 2 and 3– Day 22).

3.2.2 Secondary

Safety:

- Occurrence of study vaccine-related unsolicited non-serious AEs following each study vaccination through approximately 21 days after each study vaccination.
- Occurrence of all unsolicited non-SAEs following each study vaccination through approximately 21 days after each study vaccination.
- Occurrence of MAAEs, including NOCMCs and PIMMCs, following 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 2017 H7N9 vaccine strain at approximately 21 days after receipt of 1 dose of AS03-adjuvanted 2017 H7N9 IIV (Group 1– Day 22; Group 2 – Day 43; Group 3 – N/A).
- For HAI and Neut antibodies, percentage of subjects achieving serum HAI and Neut antibody titers ≥1:40 against the influenza 2017 H7N9 vaccine strain at baseline and approximately 21 days after receipt of 1 dose of AS03-adjuvanted 2017 H7N9 IIV (Group 1–Day 1 (baseline) and Day 22; Group 2 –Day 22 (baseline) and Day 43; Group 3 – N/A).
- GMTs of serum HAI and Neut antibodies against the influenza 2017 H7N9 vaccine virus at baseline and at approximately 21 days after receipt of 1 dose of AS03-adjuvanted 2017 H7N9 IIV. (Group 1–Day 1 (baseline) and Day 22; Group 2 –Day 22 (baseline) and Day 43; Group 3 – N/A).

3.2.3 Exploratory

Immunogenicity:

- For HAI and Neut antibodies, percentage of subjects achieving seroconversion, percentage with titer ≥1:40 and the GMTs against the 2017 H7N9 study vaccine strain approximately 21 and 180 days after 2 doses of adjuvanted 2017 H7N9 IIV, stratified by age, sex, BMI, and prior receipt of seasonal influenza vaccine(s) for Groups 1 and 2.
- For HAI and Neut antibodies, percentage of subjects achieving seroconversion, percentage with a titer ≥1:40 and the GMTs against the IIV4 vaccine strains approximately 21 and 180 days after receipt of IIV4, stratified by age, sex, BMI, and prior receipt of seasonal influenza vaccine(s).
- For HAI and Neut antibodies, percentage of subjects achieving seroconversion, percentage with titer ≥1:40, and GMTs against the 2017 H7N9 study vaccine strain at approximately 180 days after 2 doses of adjuvanted 2017 H7N9 IIV for Groups 1 and 2.
- Percentage of subjects with detectable levels of serum N1, N2 and N9 NA-specific antibody elicited by 2017 H7N9 and seasonal IIV4 vaccination, and the correlation of the NA content of 2017 H7N9 IIV and seasonal IIV4 with the elicited NA specific antibody responses at baseline and approximately 21 and 180 days after 2 doses of adjuvanted 2017 H7N9 IIV for Groups 1 and 2; and approximately 21 and 180 days after receipt of the seasonal IIV4 vaccine for all Groups.

4 STUDY DESIGN

This is a randomized, un-blinded, Phase II study in males and non-pregnant females, who are in good health, 19 to 64 years of age. This clinical trial is designed to assess the safety, reactogenicity, and immunogenicity of a pre-pandemic AS03 (GSK) adjuvanted 2017 monovalent inactivated influenza A/H7N9 vaccine (2017 H7N9 IIV) manufactured by Sanofi Pasteur (3.75 mcg of HA per dose) and Phosphate Buffered Saline (PBS) diluent, when two doses are administered 21 days apart either sequentially or simultaneously (within 15 minutes) with licensed seasonal influenza vaccine. 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 from A/Puerto Rico/8/1934 (H1N1). IIV4 will be provided through the DMID CMS, Fisher BioServices.

Subjects who are in good health and meet all eligibility criteria (including an ESR, urine or serum pregnancy test [female subjects], history and physical exam) within 28 days prior to the first vaccination or on the day of, but prior to, first vaccination, will be eligible for randomization into one of three treatment arms as shown in Table 1. Baseline 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 and 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 collected for Group 1 on Days 1 (baseline), 22, and 43, and at approximately 180 days post second adjuvanted 2017 H7N9 IIV dose (Day 202), and for Group 2 on Study Days 22 (baseline), 43, and 64, and at approximately 180 days post second 2017 H7N9 IIV adjuvanted dose (Day 223).Serological antibody assays will be performed against the vaccine viruses in IIV4 from serum samples collected at baseline (Day 1) and approximately 21 and 180 days following receipt of IIV4 (Groups 1, 2, and 3).

Novel methods for identifying and assessing alternative correlates of protection against influenza infection are needed. To assess the NA-specific antibody response to vaccination, it is first necessary to determine the NA content of inactivated influenza vaccine; this assay is under

development. If successful, the NA content in a dosage-specific manner can be correlated to the N9 NA-specific antibody responses elicited by the 2017 H7N9 IIV.

Subjects will be ineligible to participate in this trial if they have received the 2017-2018 licensed seasonal IIV (IIV3 or IIV4, including high dose vaccine for the elderly) any time prior to enrollment; IIV4 will be provided at the first study vaccination to all participants in the study.

For additional details on study procedures and evaluations and study schedule by study visits/days, see Sections 7 and 8 and Appendix A: Schedule of Study Procedures and Evaluations.

5 STUDY ENROLLMENT AND WITHDRAWAL

Approximately 150 individuals 19-64 years of age, males and non-pregnant females, who are in good health by history and meet all eligibility criteria, will be enrolled at up to 4 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 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 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, 19 -64 years of age, inclusive.
4. Are in good health[1].

[1] *As determined by medical history and physical examination 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, Emergency Room (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 beats per minute (bpm), inclusive.
7. Systolic blood pressure is 85 to 150 mmHg, inclusive (subjects <65 years of age), 85 to 160 mmHg, inclusive (subjects ≥ 65 years of age).
8. Diastolic blood pressure is 55 to 95 mmHg, inclusive.
9. ESR is less than 30 mm per hour.
10. Women of childbearing potential[2] must use 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 condoms or diaphragms* ***with*** *spermicide or foam, effective intrauterine devices, NuvaRing®, and licensed hormonal methods such as implants, injectables, or oral contraceptives ("the pill").*
11. Women of childbearing potential must have a negative urine or serum 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 principal investigator 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 principal investigator 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, 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 personal or family history of narcolepsy.
10. Have a history of GBS.
11. Have a history of convulsions or encephalomyelitis within 90 days prior to study vaccination.
12. Have a history of PIMMCs[6]

    [6]*Refer to Appendix B: List of Potentially Immune-Mediated Medical Conditions.*
13. Have a history of alcohol or drug abuse within 5 years prior to study vaccination.
14. Have any diagnosis, current or past, of schizophrenia, bipolar disease, or other psychiatric diagnosis that may interfere with subject compliance or safety evaluations.
15. 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.
16. Have taken oral or parenteral (including intra-articular) corticosteroids of any dose within 30 days prior to study vaccination.
17. Have taken high-dose inhaled corticosteroids[7] within 30 days prior to each study vaccination.

    [7]*High-dose defined per age as using inhaled high dose per reference chart https://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines/quick-reference-html#estimated-comparative-daily-doses*
18. 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.
19. Received or plan to receive a licensed, inactivated, vaccine (excluding all flu vaccines) within 14 days before or after each study vaccination.

20. Received or plan to receive the 2017-2018 inactivated seasonal flu vaccine prior to or during the clinical trial and for the remainder of the 2017-2018 season.
21. Received Ig or other blood products (with exception of Rho D Ig) within 90 days prior to each study vaccination.
22. 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.*
23. 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.*
24. 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.*
25. 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.*
26. Occupational exposure to or substantial direct physical contact[13] with birds in the past year and through the 21 days after the last 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.*
27. Female subjects who are breastfeeding or plan to breastfeed at any given time from the first study vaccination until 30 days after the last study vaccination.
28. Plan to travel outside the US (continental US, Hawaii, and Alaska) from enrollment through 21 days after the last study vaccination.

5.2 Treatment Assignment Procedures

5.2.1 Enrollment and 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 and 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 and randomly assigned to one of three treatment arms. Subjects in Groups 1 and 2 will receive three vaccinations. Subjects in Group 3 will receive IIV4 as an unblinded comparator. Subjects will be randomized with allocation 2:2:1 into three treatment arms (see Table 1), stratified by clinical site.

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.

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.

5.2.2 Masking Procedures

This is an un-blinded clinical trial.

Subjects, investigators, study personnel performing any study-related assessments following study vaccine administration are not blinded to study treatment. However, 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 SDCC and each subject's treatment assignment will be displayed in AdvantageEDC upon enrollment.

The Data and Safety Monitoring Board (DSMB) may receive data in aggregate and presented by treatment arm, including expected and observed rates of the expected AEs. The DSMB will review grouped data in the closed session only.

5.2.3 Reasons for Withdrawals and Discontinuation of Treatment

Subjects may voluntarily withdraw their consent for trial participation at any time and for any reason, without penalty.

A subject may withdraw or be withdrawn from this trial for any of the following reasons:

- Medical disease or condition, or any new clinical finding for which continued participation, in the opinion of the site principal investigator or appropriate sub-investigator, would compromise the safety of the subject, or would interfere with the subject's successful completion of this trial, or would interfere with the evaluation of responses (for example, has baseline significant laboratory abnormalities).
- Subject no longer meets eligibility criteria (see Section 5.1). 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.
- As deemed necessary by the site principal investigator or appropriate sub-investigator for noncompliance or other reasons.
- Subject withdrawal of consent.
- Subject lost to follow-up.
- Termination of this trial.
- New information becomes available that makes further participation unsafe.

The second and/or third dose will not be administered to a subject if any of the following criteria are met:

- Medical condition or medication change for which continued participation, in the opinion of the site principal investigator or appropriate sub-investigator, would pose a risk to the subject or would be likely to confound interpretation of the results.
- 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 subsequent 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 Dose 2 (Group 1 and Group 2, Day 22+7), or Dose 3 (Group 2, Day 43+7). 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 Dose 2 (Group 1 and Group 2, Day 22+7), or Dose 3 (Group 2, Day 43+7) and, 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, the subject may receive the subsequent 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 principal investigator 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 each study vaccination.
- Grade 3 clinical safety laboratory value (according to the toxicity table, Section 9.2.3) 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 next study vaccination. If the clinical safety laboratory value decreases to Grade 2 or less, the subject may receive the next study vaccination. The subsequent study vaccination should be scheduled to occur within the acceptable protocol-specified window for the Dose 2 (Group 1 and Group 2, Day 22+7), or Dose 3 (Group 2, Day 43+7). No exceptions to the protocol-specified window will be made.
- New onset of illness or condition that meets the Subject Exclusion Criteria (see Section 5.1.2).
- Hospitalization that occurs before administration of the second or third study vaccination.
- Subject no longer meets eligibility criteria (see Section 5.1). Note: 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.
- As deemed necessary by the site principal investigator or appropriate sub-investigator for noncompliance or other reasons.
- Subject refusal of further study vaccination.
- Subject withdrawal of consent.
- Subject lost to follow-up.
- Termination of this trial.
- New information becomes available that makes further participation unsafe.

5.2.4 Handling of Withdrawals and Discontinuation of Treatment

The primary reason for withdrawal from this trial will be recorded on the Study Status data collection form (DCF). Subjects will be encouraged to complete the Early Termination Visit. The Early Termination Visit procedures are listed in Section 8.5.

Although subjects are free to withdraw at any time or may be withdrawn by the site principal investigator or appropriate sub-investigator at any time (see Section 5.2.3), those subjects do not receive Dose 2 or Dose 3 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 21 days and 180 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 and 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, extensive effort (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.

Subjects who withdraw, or are withdrawn or terminated from this trial, or are lost to follow-up after signing the informed consent form (ICF), randomization, and receipt of study vaccine will not be replaced. However, if a subject withdraws after signing the ICF, but before randomization and/or receipt of study vaccine, they may be replaced.

5.2.5 Termination of Study

Although the sponsor has every intention of completing this trial, it reserves the right to terminate this trial at any time for clinical or administrative reasons. Reasons for termination include, but are not limited to, study closure due to DSMB review and recommendation and at the discretion of DMID.

6 STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

6.1 Study Product Description

2017 H7N9 IIV

Sanofi Pasteur has developed a monovalent 2017 H7N9 IIV manufactured from a reverse genetics-derived reassortant virus containing the HA and NA from influenza A/Hong Kong/125/2017 (H7N9) and the PB2, PB1, PA, NP, M and NS from A/Puerto Rico/8/1934 (H1N1). The manufacturing process for the production of this monovalent 2017 A/H7N9 IIV is similar to the manufacturing process used to produce the licensed IIV Fluzone® family of products.

The HA content of the A/H7N9 vaccine formulation has been determined by [redacted] In this clinical trial, the labeling of the original [redacted] The vaccine preparation has been adjusted to [redacted] The final vaccine preparation is [redacted]

PBS diluent

The PBS diluent was produced in accordance with the commercial process utilized in manufacture of [redacted] buffer/diluent for the formulation of Fluzone®, influenza virus vaccine.

AS03 Adjuvant [Adjuvant System AS(03)]

AS03 is GSK's proprietary [redacted]

Fluzone® Quadrivalent Influenza Vaccine (IIV4)

IIV4 manufactured by Sanofi Pasteur for IM injection is an inactivated influenza vaccine, prepared from influenza viruses propagated in embryonated chicken eggs. Fluzone® Quadrivalent is formulated to contain HA of each of the following four influenza strains recommended for the 2017-2018 influenza season: A/Michigan/45/2015 X-275 (H1N1), A/Hong Kong/4801/2014 X-263B (H3N2), B/Phuket/3073/2013 (B Yamagata lineage), and B/Brisbane/60/2008 (B Victoria lineage). The single-dose, pre-filled syringe (0.5 mL)

without thimerosal, clear plunger rod, without needle will be supplied as package of 10 syringes.

6.1.1 Acquisition

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

The PBS diluent will be provided by Sanofi Pasteur under contract to BARDA/DHHS.

AS03 adjuvant will be provided by GSK under contract to BARDA/DHHS.

Fluzone® Quadrivalent Influenza Vaccine (IIV4) will be provided through the DMID Clinical Materials Services (CMS) Contract, Fisher BioServices.

Upon request by DMID, 2017 H7N9 IIV, PBS diluent, and AS03 adjuvant will be transferred to the following address:

DMID Clinical Materials Services Contract
Fisher BioServices
20439 Seneca Meadows Parkway
Germantown, MD 20876
Phone: 240-477-1350
Fax: 240-477-1360
Email: DMID.CMS@ThermoFisher.com

Sterile empty vials will be obtained by the DMID Clinical Materials Services (CMS), Fisher BioServices.

2017 H7N9 IIV, AS03 adjuvant, PBS diluent, IIV4 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 principal investigator require additional 2017 H7N9 IIV, PBS diluent, AS03 adjuvant, IIV4 or sterile empty vials during this trial, further instructions are provided in the protocol-specific MOP.

6.1.2 Formulation, Storage, Packaging, and Labeling

2017 H7N9 IIV

Investigational influenza virus A/Hong Kong vaccine (H7N9), a monovalent type A inactivated vaccine for IM use, is a sterile suspension prepared from pandemic influenza virus candidate vaccine propagated in embryonated chicken eggs. The vaccine contains no preservative (thimerosal). No components of this vaccine contain latex. It is essentially clear and slightly opalescent in color and is supplied in single-dose glass vials. The vials must be stored at 2°C to 8°C (36°F to 46°F). Do not freeze. Vials will be provided with latex-free stoppers.

The specific mixing instructions are included in the MOP to achieve specific doses.

Please note the difference [redacted] in the vial.

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

PBS Diluent

The [redacted] is provided as [redacted] It is essentially [redacted], and should be stored [redacted] The PBS diluent will be provided in [redacted]

AS03 Adjuvant [Adjuvant System (03)]

The AS03 adjuvant is supplied as a preservative-free, oil-in-water, whitish to yellowish homogenous milky liquid emulsion in single-use vials. The vials must be stored at 2°C to 8°C (36°F to 46°F). Do not freeze. Vials will be provided with latex-free stoppers.

Fluzone® Quadrivalent Influenza Vaccine (IIV4) Fluzone® Quadrivalent Influenza Vaccine, Sanofi Pasteur, pre-filled syringes, thimerosal-free, 0.5 mL single-dose prefilled syringes (pack of 10). The pre-filled syringes must be stored at 2°C to 8°C (36°F to 46°F). 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 IBs for the 2017 H7N9 IIV, AS03 adjuvant, and IIV4 as well as in the protocol-specific MOP.

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

6.1.3 Study Product Storage and Stability Procedures

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 principal investigator 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 principal investigator 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.

6.2 Dosage, Preparation, and Administration of Study Intervention/ Investigational Product

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, IIV4 and AS03 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 principal investigator 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 vaccine, PBS diluent, or the AS03 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, visually inspect the 2017 H7N9 IIV/PBS diluent plus adjuvant admixture prior to use. The admixture will be milky in appearance. If it appears to have been damaged, contaminated or discolored, contain visible particulate matter, or if there are any concerns regarding its integrity, do NOT use it. The affected 2017 H7N9 IIV/PBS diluent plus

adjuvant admixture must be quarantined at room temperature and labeled as 'Do Not Use' (until further notice). The site principal investigator 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 2017 H7N9 IIV/PBS diluent plus adjuvant admixture can be used. If it cannot be used, the site will receive specific instructions on how to send the 2017 H7N9 IIV/PBS diluent plus adjuvant admixture to the DMID CMS or destroy it on site. If the 2017 H7N9 IIV/PBS diluent plus adjuvant admixture is unusable, the participating VTEU sites' research pharmacist will prepare another vial. Additional instructions for quarantine and DMID contact information are provided in the protocol-specific MOP.

For those doses that must be admixed, the 2017 H7N9 IIV/PBS diluent plus adjuvant admixture, once mixed, must be stored at room temperature in an upright position and must be used within 8 hours. Gently invert the final mixed vial 5 to 7 times immediately before the single dose is withdrawn. **Do not shake the final mixed vial.** Only one dose should be withdrawn from the final mixed vial.

Study vaccine administration will be performed by a study personnel member who is credentialed to administer vaccines and may also participate in dose preparation, and may be involved in study-related assessments or have subject contact for data collection following study vaccine administration.

For treatment assignment per Group, refer to Table 1.

On study Day 1, Groups 1-3 will receive Dose 1. For Group 1, Dose 1 consists of one vaccination of AS03-adjuvanted 2017 H7N9 IIV and one vaccination of licensed seasonal IIV4 in the deltoid muscle of opposite arms. This is the only Group, and the only study Day for Group 1, that subjects will receive two vaccines administered IM simultaneously (within 15 minutes of each other). On Day 1, Group 2 and Group 3 will receive one vaccination of IIV4 administered IM in the deltoid muscle of the subject's preferred arm.

On study Day 22, Group 1 will receive the second dose of adjuvanted 2017 H7N9 IIV, and Group 2 will receive the first dose of adjuvanted 2017 H7N9 IIV.

On Day 43, Group 2 will receive the second dose of adjuvanted 2017 H7N9 IIV.

All study vaccinations will be administered as a 0.5 mL IM injection. The site of each injection (right and/or left arm) will be recorded on the appropriate DCF.

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 1 mL 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.

Dose calculations are based on the actual HA content per 0.5 mL. Each 0.5 mL dose of AS03 adjuvanted study vaccine contains one 0.25 mL dose of AS03 adjuvant.

For Fluzone Quadrivalent, before administering a dose of vaccine, shake the prefilled syringe. Aseptic technique will be used for the administration of each dose of study vaccine using a disposable sterile needle appropriate in length for each subject.

Subjects will be observed in the clinic for at least 20 minutes after the vaccination (for Group 1, Dose 1, the 20 minute clock will start after receipt of the second vaccination). The vaccination site will be examined, post-administration reactogenicity assessments will be performed, and any AE/SAEs will be recorded on the appropriate DCF prior to discharge from the clinic.

6.3 Modification of Study Intervention/Investigational Product for a Subject

There will be no dose modifications. If a subject's study vaccination is deferred, it should be rescheduled to occur within the acceptable protocol-specified window for that visit. No exceptions to the protocol-specified window will be made.

6.4 Accountability Procedures for the Study Intervention/ Investigational Product

After receipt of the 2017 H7N9 IIV, PBS diluent, AS03 adjuvant, IIV4 and sterile empty vials, the site principal investigator is responsible for study product distribution and disposition, and has ultimate responsibility for study product accountability. The site principal investigator may 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 DCF. All study product(s), including the amount of 2017 H7N9 IIV, AS03 adjuvant, IIV4 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, AS03 adjuvant, IIV4 and admixture will be retained until monitored and released for disposition as applicable. The pre-filled IIV4 single use syringe will be disposed of per site processes once the vaccine is administered. This can occur on an ongoing basis for used vials of 2017 H7N9 IIV, AS03 adjuvant, IIV4 and admixture. Used vials of A/H7N9 vaccine, AS03 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, AS03 adjuvant, IIV4 and sterile empty vials will be determined by DMID and communicated to the participating VTEU sites by the DMID Clinical Project Manager.

6.5 Assessment of Subject Compliance with Study Intervention/ Investigational Product

Study product will be administered to subjects by a study vaccine administrator via IM injection at all dosing times according to subject treatment assignment and as described in Section 6.2. Thus, subject compliance is not anticipated to be an issue. There will be no dose schedule modifications, other than within the protocol-specified windows, as described in Section 6.3.

6.6 Concomitant Medications/Treatments

Administration of any medications, therapies, or vaccines will be recorded on the appropriate DCF. Concomitant medications will include all current medications and medications taken in the 60 days prior to signing the ICF through approximately 21 days after the last study vaccination or early termination (if prior to 21 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 21 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 principal investigator 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 STUDY PROCEDURES AND 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. Subjects will also be queried regarding a personal history and family history of narcolepsy. 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 6.6.

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: skin, head and neck, lungs, heart, liver, spleen, extremities, lymph nodes, and nervous system, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site principal investigator or sub-investigator. At follow-up visits after the first, second, and/or third study vaccinations, 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 principal investigator 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 (Day 1, and approximately Days 22 and 43, as applicable to study group). 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 (itching), ecchymosis (bruising),

erythema (redness), induration (hardness), edema (swelling), pain, and tenderness as well as systemic reactions including fever, feverishness (chills/shivering/sweating), fatigue (tiredness), malaise (general unwell feeling), myalgia (body aches/muscular pain exclusive of the injection site), arthralgia (joint pain exclusive of the injection site), 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 (see Section 5.2.3).

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 DCF 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).

7.2 Laboratory Evaluations

7.2.1 Clinical Laboratory Evaluations

Urine or serum pregnancy tests will be performed locally by site laboratory 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. ESR will be collected from each subject at screening (optional) (within 28 days prior to the first study vaccination) or on Day 1 prior to study vaccination to confirm trial eligibility. To be eligible for participation in this trial and receipt of the first study vaccination, the subject's ESR evaluation must be confirmed to meet the eligibility criteria as outlined in the Subject Inclusion Criteria (see Section 5.1.1).

- The ESR evaluation will be performed locally by the site. A venous blood sample (approximately 4 mL) will be collected from each subject at the baseline visit.

Clinical safety laboratory parameters (WBC, Hgb, PLT, ALT, T. Bili, 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 each of 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 ESR as well as clinical safety laboratory evaluations is presented in Table 2.

7.2.2 Special Assays or Procedures

Immunogenicity

Assays to determine serum levels of HAI and Neut antibodies will be performed at Southern Research. Immunogenicity testing will include performing HAI and Neut antibody assays against the 2017 H7N9 vaccine virus on serum samples collected for Group 1 on Days 1 (baseline), 22, and 43, and at approximately 180 days post second 2017 H7N9 IIV dose (Day 202), and for Group 2 on Days 22 (baseline), 43, and 64, and at approximately 180 days post second 2017 H7N9 IIV dose (Day 223). Serological antibody assays will be performed against the vaccine viruses in IIV4 from serum samples collected at baseline (Day 1) and approximately 21 and 180 days following receipt of IIV4 (Groups 1, 2 and 3). Subjects who withdraw early will have HAI and Neut antibody assays run on available sera.

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. 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.

After all subjects in Groups 1 and 2 have completed the Day 64 clinic visit (Visit 08 for Group 1 and Visit 10 for Group 2), samples for the HAI and Neut analysis will be shipped from the DMID CMS to Southern Research. Following the last subject's clinic visit at 180 days after the last study vaccination (Visit 10 for Group 1 and Visit 12 for Group 2), samples for the final HAI and Neut analysis will be shipped from the DMID CMS to Southern Research.

For all Groups, serological antibody assays will be performed against the vaccine viruses in IIV4 from serum samples collected at baseline (Study Day 1), and 21 and 180 days following receipt of IIV4.

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 out of 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 opt out option.

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

Table 2 a

Group 1 Venipuncture Volumes (mL):

Vaccination Period

Study Visit Number	**V00**	**V01**	**V03**	**V04**	**V06**	**V07**	**Total (mL)**
Study Day post Dose 1 (H7N9 + IIV4)	**Screening (Optional) D -28 to -1**	**Enrollment Dose 1 D1**	**D8+2d**	**D22+7d**	**D29**	**D43**	
Study Day post Dose 2 (H7N9)				**Dose 2 D1**	**D8+2d**	**D22+7d**	
Study Vaccination		X		X			
ESR	4^	4^*					**4**
Clinical Baseline and Safety Laboratory Evaluations~		10†	10	10†	10		**40**
Immunogenicity Assays		10†		10†		10	**30**
Serum Sample for Future Research#		10†	10	10†	10	10	**50**
Total (mL)	**(4) 0**	**(30) 34**	**20**	**30**	**20**	**20**	**124**

^ Drawn up to 28 days prior to study vaccination. Results must be known and confirmed to meet the eligibility criterion prior to randomization and first study vaccination.

~ Includes WBC, Hgb, PLT, ALT, T. Bili, Cr.

Sites may elect to allow subjects to consent to study participation but to have the option to opt out of 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 opt out option.† All blood drawn immediately prior to study vaccination.

* Not required if done at the optional screening visit

Group 1 Venipuncture Volumes (mL):

Follow-up Period

Study Visit Number	**V08**	**V09**	**V10**	**Total (mL)**
Study Day post Dose 1 (H7N9 + IIV4)	**D64**	**D181 ±14**	**D202**	
Study Day post Dose 2 (H7N9)	**D43+7**		**D181±14**	
Clinical Safety Laboratory Evaluations~				
Immunogenicity Assays		10	10	**20**
Serum Sample for Future Research#	10	10	10	**30**
Total (mL)	**10**	**20**	**20**	**50**

^ Drawn up to 28 days prior to study vaccination. Results must be known and confirmed to meet the eligibility criterion prior to randomization and first study vaccination.

~ Includes WBC, Hgb, PLT, ALT, T. Bili, Cr.

Sites may elect to allow subjects to consent to study participation but to have the option to opt out of 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 opt out option.

† All blood drawn immediately prior to study vaccination.

* Not required if done at the optional screening visit

Table 2 b

Group 2 Venipuncture Volumes (mL):

Vaccination Period

Study Visit Number	**V00**	**V01**	**V03**	**V04**	**V06**	**V07**	**Total (mL)**
Study Day post Dose 1 (IIV4)	**Screening (Optional) D -28 to -1**	**Enrollment and Dose 1 D1**	**D8+2d**	**D22+7d**	**D29**	**D43**	
Study Day post Dose 2 (H7N9)				**Dose 2 D1**	**D8+2d**	**D22+7d**	
Study Day post Dose 3 (H7N9)						**Dose 3 D1**	
Study Vaccination		X		X		X	
ESR	4^	4^*					**4**
Clinical Baseline and Safety Laboratory Evaluations~		10†	10	10†	10	10†	**50**
Immunogenicity Assays		10†		10†		10†	**30**
Serum Sample for Future Research#		10†	10	10†	10	10†	**50**
Total (mL)	**(4) 0**	**(30) 34**	**20**	**30**	**20**	**30**	**134**

^ Drawn up to 28 days prior to study vaccination. Results must be known and confirmed to meet the eligibility criterion prior to randomization and first study vaccination.

~ Includes WBC, Hgb, PLT, ALT, T. Bili, Cr.

Sites may elect to allow subjects to consent to study participation but to have the option to opt out of 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 opt out option.

† All blood drawn immediately prior to study vaccination.

* Not required if done at the optional screening visit

Group 2 Venipuncture Volumes (mL):

Follow-up Period

Study Visit Number	**V09**	**V10**	**V11**	**V12**	**Total (mL)**
Study Day post Dose 1 (IIV4)	**D50**	**D64**	**D181 ±14**	**D223**	
Study Day post Dose 2 (H7N9)	**D29**	**D43**		**D202**	
Study Day post Dose 3 (H7N9)	**D8+2d**	**D22+7d**		**D181±14**	
Clinical Safety Laboratory Evaluations~	10				**10**
Immunogenicity Assays		10	10	10	**30**
Serum Sample for Future Research#	10	10	10	10	**40**
Total (mL)	**20**	**20**	**20**	**20**	**80**

~ Includes WBC, Hgb, PLT, ALT, T. Bili, Cr.

Sites may elect to allow subjects to consent to study participation but to have the option to opt out of 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 opt out option.

Table 2 c

Group 3 Venipuncture Volumes (mL):

Vaccination and Follow-up

Study Visit Number	**V00**	**V01**	**V03**	**V04**	**V05**	**V06**	**V07**	**Total (mL)**
Study Day post Dose 1 (IIV4)	**Screening (Optional) D -28 to -1**	**Enrollment and Dose 1 D1**	**D8+2d**	**D22+7d**	**D43+7d**	**D64+7d**	**D181±14 d**	
Study Vaccination		X						
ESR	4^	4^*						**4**
Clinical Baseline and Safety Laboratory Evaluations~		10†	10					**20**
Immunogenicity Assays		10†		10			10	**30**
Serum Sample for Future Research#		10†	10	10	10	10	10	**60**
Total (mL)	**(4) 0**	**(30) 34**	**20**	**20**	**10**	**10**	**20**	**114**

^ Drawn up to 28 days prior to study vaccination. Results must be known and confirmed to meet the eligibility criterion prior to randomization and first study vaccination.

~ Includes WBC, Hgb, PLT, ALT, T. Bili, Cr.

Sites may elect to allow subjects to consent to study participation but to have the option to opt out of 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 opt out option.

† All blood drawn immediately prior to study vaccination.

* Not required if done at the optional screening visit

7.2.3 Specimen Preparation, Handling, and Shipping

7.2.3.1 Instructions for Specimen Preparation, Handling, and Storage

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

7.2.3.2 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 STUDY SCHEDULE

Complete study schedule details listed by type of visit are described below. Refer also to Sections 4 and 7 and Appendix A: Schedule of Study Procedures and Evaluations. For detailed information regarding the study schedule for discontinued subjects, please reference the MOP–Discontinued Subjects Remaining on Study.

8.1 Screening (Optional) and Enrollment Visits, All Groups

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

- 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 and second study vaccinations for Group 1, and the first study vaccination for Groups 2 and 3.
- 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 previous two seasons, what type (inactivated or live attenuated), and approximate date of vaccination will be recorded on the appropriate DCF, if known. Prior receipt of licensed seasonal influenza vaccine in the 2017/2018 season is exclusionary (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 principal investigator or sub-investigator.
- A urine or serum pregnancy test may be performed on all women of childbearing potential. Results must be negative to ensure eligibility.
- Approximately 4 mL of venous blood will be collected for ESR, and performed locally by the site. The ESR value must be confirmed as less than 30 mm per hour prior to randomization and the first vaccination.

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

Group 1 (First and Second Study Vaccinations): AS03 adjuvanted 2017 H7N9 IIV + IIV4

Groups 2 and 3 (First Study Vaccination): IIV4

- 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 vaccination.
- Eligibility criteria, including results of the ESR will be reviewed.
- 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 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 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 vaccination.
- Vital signs, including oral temperature, pulse, and blood pressure, will be obtained to ensure eligibility prior to the first vaccination. Vital signs assessed on Day 1 prior to the first 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 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 principal investigator or sub-investigator.

- A urine or serum pregnancy test will be performed within 24 hours prior to the first vaccination on all women of childbearing potential. Results must be negative and known prior to randomization and first vaccination.
- Subjects will be enrolled in AdvantageEDC^{SM} and assigned randomly to a treatment arm prior to the first vaccination.
- Pre-administration reactogenicity assessments will be performed prior to the first vaccination to establish baseline.
- Approximately 10 mL of venous blood will be collected immediately prior to the first vaccination for baseline serum antibody assays.
- Approximately 10 mL of venous blood will be collected immediately prior to the first vaccination for baseline clinical safety labs (WBC, Hgb, PLT, ALT, T. Bili, Cr), and performed by the central (clinical) laboratory. The results from this blood draw will not be available or reviewed prior to the vaccination, and will serve as a safety baseline assessment only.
- Approximately 10 mL of venous blood will be collected prior to vaccination for future research from subjects who consent, 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 form allows the option to choose that option.
- Subjects will then receive a single dose of vaccine (Group 1 will receive 2 vaccines) via IM injection into the deltoid muscle of the preferred arm, or if randomized to Group 1, in both arms within 15 minutes of each other. The site of injection (right and/or left arm) and time of administration will be recorded on the appropriate DCF. Subjects will be observed in the clinic for at least 20 minutes after the vaccination. The vaccination site will be examined, post-administration reactogenicity assessments will be performed, and any AE/SAEs will be recorded on the appropriate DCF 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 vaccination(s). 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.

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

Group 1 (First and Second Study Vaccinations): AS03 adjuvanted 2017 H7N9 IIV + IIV4

Groups 2 and 3 (First Study Vaccination): IIV4

- 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 vaccination.
- Demographic information will be obtained by interview of subjects.
- Complete medical history will be obtained by interview of subjects prior to the first vaccination to ensure eligibility.
- All concomitant medications taken within 60 days prior to signing the ICF will be reviewed with subjects and reported in the eCRF prior to the first vaccination. Medications reported in the eCRF are limited to those taken within 30 days prior to the first vaccination.
- Subject receipt of licensed seasonal influenza vaccine over the previous two seasons, what type (inactivated or live attenuated), and approximate date of vaccination will be recorded on the appropriate DCF, if known. Prior receipt of 2017-2018 licensed seasonal influenza vaccine is exclusionary.
- 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 the first vaccination. Vital signs assessed on Day 1 prior to the first 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 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 principal investigator or sub-investigator.

- Approximately 4 mL of venous blood will be collected for ESR, and performed locally by the site. The ESR value must be confirmed as less than 30 mm per hour prior to randomization and first vaccination.
- Eligibility criteria, including results of ESR evaluation, will be reviewed with subjects prior to the first vaccination to ensure continued eligibility.
- A urine or serum pregnancy test will be performed within 24 hours prior to the first vaccination on all women of childbearing potential. Results must be negative and known prior to randomization and first vaccination.
- Subjects will be enrolled in AdvantageEDC^{SM} and assigned randomly to a treatment arm prior to the first vaccination.
- Pre-administration reactogenicity assessments will be performed prior to the first vaccination to establish baseline.
- Approximately 10 mL of venous blood will be collected immediately prior to the first vaccination for baseline serum antibody assays.
- Approximately 10 mL of venous blood will be collected immediately prior to the first vaccination for baseline clinical safety labs (WBC, Hgb, PLT, ALT, T. Bili, Cr), and performed by the central (clinical) laboratory. The results from this blood draw will not be available or reviewed prior to vaccination, and will serve as a safety baseline assessment only.
- Approximately 10 mL of venous blood will be collected prior to vaccination for future research from subjects who consent, 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 form allows the option to choose that option.
- Subjects will then receive a single dose of study vaccine (Group 1 will receive 2 vaccines) via IM injection into the deltoid muscle of the preferred arm, or if randomized to Group 1, in both arms within 15 minutes of each other. The site of injection (right and/or left arm) and time of administration will be recorded on the appropriate DCF. Subjects will be observed in the clinic for at least 20 minutes after the vaccination. The vaccination site will be examined, post-administration reactogenicity assessments will be performed, and any AE/SAEs will be recorded on the appropriate DCF 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 vaccination(s). 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.

8.2 Follow-up Visits, Group 1

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

8.2.1 Visit 02, Day 4, Memory Aid Review, Phone Call (Window: 3 (±1) days post Dose 1)

Study personnel will contact subjects by phone to solicit any AE/SAE 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.

8.2.2 Visit 03, Day 8, Clinic Visit (Window: 7 (+2) days post first Dose 1))

- 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) will be recorded on the appropriate DCF.

- All AE/SAEs will be recorded on the appropriate DCF.
- 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 principal investigator or sub-investigator.
- The H7N9 and IIV4 vaccination sites will be examined.
- Approximately 10 mL of venous blood will be collected for 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 future research from subjects who consent, 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 form allows the option to choose that option.

8.2.3 Visit 04, Day 22, Dose 2, Clinic Visit (Window: 21 (+7) days post Dose 1)

- Eligibility criteria will be reviewed with subjects prior to the vaccination to ensure continued eligibility.
- For a subject to receive the vaccination, refer to section 5.2.3 for subsequent dose 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 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 DCF prior to the vaccination.
- All AE/SAEs will be recorded on the appropriate DCF.

- Vital signs, including oral temperature, pulse, and blood pressure, will be obtained prior to the 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 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 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 principal investigator or sub-investigator.
- A urine or serum pregnancy test will be performed within 24 hours prior to the study vaccination on all women of childbearing potential. Results must be negative and known prior to the vaccination.
- Pre-administration reactogenicity assessments will be performed prior to the study vaccination to establish baseline.
- Approximately 10 mL of venous blood will be collected immediately prior to the vaccination for 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 immediately prior to the vaccination for serum antibody assays.
- Approximately 10 mL of venous blood will be collected immediately prior to the vaccination for future research from subjects who consent, 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 form 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. If the subject has no preference, the second dose of adjuvanted 2017 H7N9 IIV may be given in either arm as long as there is no hindrance of the reactogenicity assessment. The site of injection (right or left arm) and time of administration will be recorded on the appropriate DCF. Subjects will be observed in the clinic for at least 20 minutes after the vaccination. The vaccination site will be examined, post-administration reactogenicity assessments will be performed, and any AE/SAEs will be recorded on the appropriate DCF 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 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.

8.2.4 Visit 05, Day 25, Memory Aid Review, Phone Call (Window: 3 (±1) days post Dose 2)

Study personnel will contact subjects by phone to solicit any AE/SAE 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 Dose 2, AEs will be limited to SAEs and MAAEs, including NOCMCs and PIMMCs.

8.2.5 Visit 06, Day 29, Clinic Visit (Window: 7 (+2) days post Dose 2)

- 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) will be recorded on the appropriate DCF.
- All AE/SAEs will be recorded on the appropriate DCF. Note: for subjects who discontinued from the receipt of Dose 2, AEs will be limited to SAEs and 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 principal investigator or sub-investigator.

- The Dose 2 (third vaccination) site will be examined.
- Approximately 10 mL of venous blood will be collected for 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 future research from subjects who consent, 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 form allows the option to choose that option.

8.2.6 Visit 07, Day 43, Safety Follow-up Clinic Visit (Window: 21 (+7) days post Dose 2)

- 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) will be recorded on the appropriate DCF.
- All AE/SAEs will be recorded on the appropriate DCF.
- 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 principal investigator or sub-investigator.
- Approximately 10 mL of venous blood will be collected for serum antibody assays.
- Approximately 10 mL of venous blood will be for future research from subjects who consent, 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 form allows the option to choose that option.

8.2.7 Visit 08, Day 64, Safety Follow-up, Clinic Visit (Window: 42 days (+7) days post Dose 2)

- 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.

- Concomitant medications (solicitation only 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) will be recorded on the appropriate DCF.

- All SAEs and MAAEs, including NOCMs and PIMMCs, will be recorded on the appropriate DCF.

- 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 principal investigator or sub-investigator.

- Approximately 10 mL of venous blood will be collected for future research from subjects who consent to collection of serum for future research.

8.2.8 Visit 09, Day 181, Safety Follow-up, Clinic Visit (Window: 180 (±14) days post Dose 1)

- 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.

- Concomitant medications (solicitation only 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) will be recorded on the appropriate DCF.

- AEs limited to MAAEs, including NOCMCs and 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 principal investigator 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, 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 form allows the option to choose that option.

8.2.9 Visit 10, Day 202, Safety Follow-up, Clinic Visit (Window: 180 (±14) days post Dose 2)

- 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.

- Concomitant medications (solicitation only 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) will be recorded on the appropriate DCF.AEs limited to MAAEs, including NOCMCs and 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 principal investigator 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, 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 form allows the option to choose that option.

8.2.10 Visit 11, Day 387, Safety Follow-up, Phone Call (Window: 365 (±14) days post Dose 2)

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.

8.3 Follow-up Visits, Group 2

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

8.3.1 Visit 02, Day 4, Memory Aid Review, Phone Call (Window: 3 (±1) days post Dose 1)

Study personnel will contact subjects by phone to solicit any AE/SAE 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.

8.3.2 Visit 03, Day 8, Clinic Visit (Window: 7 (+2) days post Dose 1)

- 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) will be recorded on the appropriate DCF.
- All AE/SAEs will be recorded on the appropriate DCF.

- 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 principal investigator or sub-investigator.

- The first vaccination site will be examined.

- Approximately 10 mL of venous blood will be collected for 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 future research from subjects who consent, 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 form allows the option to choose that option.

8.3.3 Visit 04, Day 22, Dose 2, Clinic Visit (Window: 21 (+7) days post first study vaccination)

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

- For a subject to receive the vaccination, refer to section 5.2.3 for subsequent dose 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 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 DCF prior to the vaccination.

- All AE/SAEs will be recorded on the appropriate DCF.

- Vital signs, including oral temperature, pulse, and blood pressure, will be obtained prior to the 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 Dose 2 and are being followed for safety.

- A targeted physical examination, including an assessment for signs suggestive of PIMMCs, may be performed prior to the 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 principal investigator or sub-investigator.

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

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

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

- Approximately 10 mL of venous blood will be collected immediately prior to the vaccination for future research from subjects who consent, 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 form 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 vaccination may be given in either 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 DCF. Subjects will be observed in the clinic for at least 20 minutes after the vaccination. The vaccination site will be examined, post-administration reactogenicity assessments will be performed, and any AE/SAEs will be recorded on the appropriate DCF 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 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.

8.3.4 Visit 05, Day 25, Memory Aid Review, Phone Call (Window: 3 (±1) days post Dose 2)

Study personnel will contact subjects by phone to solicit any AE/SAE 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 Dose 2, AEs will be limited to SAEs and MAAEs, including NOCMCs and PIMMCs.

8.3.5 Visit 06, Day 29, Clinic Visit (Window: 7 (+2) days post Dose 2)

- 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) will be recorded on the appropriate DCF.
- All AE/SAEs will be recorded on the appropriate DCF. Note: for subjects who discontinued from the receipt of Dose 2, AEs will be limited to SAEs and 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 principal investigator or sub-investigator.

- The second vaccination site will be examined.

- Approximately 10 mL of venous blood will be collected for 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 future research from subjects who consent, 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 form allows the option to choose that option.

8.3.6 Visit 07, Day 43, Dose 3, Clinic Visit (Window: 21 (+7) days post Dose 2)

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

- For a subject to receive the third vaccination, refer to section 5.2.3 for subsequent dose 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 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 DCF.

- Vital signs, including oral temperature, pulse, and blood pressure, will be obtained prior to the 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 Dose 3 and are being followed for safety.

- All AE/SAEs will be recorded on the appropriate DCF. Note: Vital signs are not required for subjects who are discontinued from receipt of Dose 3 and are being followed for safety.

- 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 principal investigator or sub-investigator.

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

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

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

- Approximately 10 mL of venous blood will be collected immediately prior to the vaccination for future research from subjects who consent, 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 form 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 third vaccination may be given in either 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 DCF. Subjects will be observed in the clinic for at least 20 minutes after the vaccination. The third vaccination site will be examined, post-administration reactogenicity assessments will be performed, and any AE/SAEs will be recorded on the appropriate DCF 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 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.

8.3.7 Visit 08, Day 46, Memory Aid Review, Phone Call (Window: 3 (±1) days post Dose 3)

Study personnel will contact subjects by phone to solicit any AE/SAE 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 Dose 3, AEs will be limited to SAEs and MAAEs, including NOCMCs and PIMMCs.

8.3.8 Visit 09, Day 50, Clinic Visit (Window: 7 (+2) days post Dose 3)

- 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) will be recorded on the appropriate DCF.
- All AE/SAEs will be recorded on the appropriate DCF. Note: for subjects who discontinued from the receipt of Dose 3, AEs will be limited to SAEs and 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 principal investigator or sub-investigator.

- The third vaccination site will be examined.

- Approximately 10 mL of venous blood will be collected for 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 future research from subjects who consent, 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 form allows the option to choose that option.

8.3.9 Visit 10, Day 64, Safety Follow-up, Clinic Visit (Window: 21 (+7) days post Dose 3)

- 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) will be recorded on the appropriate DCF.

- All AE/SAEs will be recorded on the appropriate DCF. Note: for subjects who discontinued from the receipt of Dose 3, AEs will be limited to SAEs and 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 principal investigator 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, 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 form allows the option to choose that option.

8.3.10 Visit 11, Day 181, Safety Follow-up, Clinic Visit (Window: 180 (±14) days post Dose 1)

- 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.

- Concomitant medications (solicitation only 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) will be recorded on the appropriate DCF.

- AEs 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 principal investigator 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, 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 form allows the option to choose that option.

8.3.11 Visit 12, Day 223, Safety Follow-up, Clinic Visit (Window: 180 (±14) days post Dose 3)

- 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.

- Concomitant medications (solicitation only 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) will be recorded on the appropriate DCF.

- AEs 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 principal investigator 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, 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 form allows the option to choose that option.

8.3.12 Visit 13, Day 408, Safety Follow-up, Phone Call (Window: 365 (±14) days post Dose 3)

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.

8.4 Follow-up Visits, Group 3

Follow-up visits are scheduled in reference to the vaccination date that is indicated for each visit window.

8.4.1 Visit 02, Day 4, Memory Aid Review, Phone Call (Window: 3 (±1) days post dose)

Study personnel will contact subjects by phone to solicit any AE/SAE 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.

8.4.2 Visit 03, Day 8, Clinic Visit (Window: 7 (+2) days post dose)

- 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) will be recorded on the appropriate DCF.
- All AE/SAEs will be recorded on the appropriate DCF.
- 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 principal investigator or sub-investigator.
- The vaccination site will be examined.
- Approximately 10 mL of venous blood will be collected for 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 future research from subjects who consent, 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 form allows the option to choose that option.

8.4.3 Visit 04, Day 22, Safety Follow-up, Clinic Visit (Window: 21 (+7) days post dose)

- 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) will be recorded on the appropriate DCF.

- All AE/SAEs will be recorded on the appropriate DCF.

- 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 principal investigator 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, 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 form allows the option to choose that option.

8.4.4 Visit 05, Day 43, Safety Follow-up, Clinic Visit (Window: 42 (+7) days post dose)

- 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.

- Concomitant medications (solicitation only 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) will be recorded on the appropriate DCF.

- All SAEs and MAAEs, including NOCMs and PIMMCs, will be recorded on the appropriate DCF. 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 principal investigator or sub-investigator.

- Approximately 10 mL of venous blood will be collected for future research from subjects who consent, 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 form allows the option to choose that option.

8.4.5 Visit 06, Day 64, Safety Follow-up, Clinic Visit (Window: 63 (+7) days post dose)

- 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.

- Concomitant medications (solicitation only 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) will be recorded on the appropriate DCF.

- All SAEs and MAAEs, including NOCMs and PIMMCs, will be recorded on the appropriate DCF. 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 principal investigator or sub-investigator.

- Approximately 10 mL of venous blood will be collected for future research from subjects who consent, 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 form allows the option to choose that option.

8.4.6 Visit 07, Day 181, Safety Follow-up, Clinic Visit (Window: 180 (±14) days post dose)

- 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.

- Concomitant medications (solicitation only 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) will be recorded on the appropriate DCF.

- All SAEs and MAAEs, including NOCMs and PIMMCs, will be recorded on the appropriate DCF. 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 principal investigator 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, 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 form allows the option to choose that option.

8.4.7 Visit 08, Day 366, Safety Follow-up, Phone Call (Window: 365 (±14) days post dose)

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.

8.5 Early Termination Visit (if needed)

The following activities will be performed at the early termination visit on subjects who withdraw, 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 DCF (if within 21 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 vaccination.

- All AE/SAEs will be recorded on the appropriate DCF. AEs will be limited to SAEs and MAAEs, including NOCMCs and PIMMCs, that have occurred since the previous clinic visit or contact will be solicited (if after 21 days after the last 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 principal investigator or sub-investigator.

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

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

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

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

- Approximately 10 mL of venous blood will be collected for future research from subjects who consent (if within 21 days after the last vaccination).

8.6 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 vaccination).

- All concomitant medications will be recorded on the appropriate DCF (if within 21 days after the last 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 vaccination.

- All AE/SAEs will be recorded on the appropriate DCF. AEs will be limited to SAEs and MAAEs, including NOCMCs and PIMMCs, if after 21 days after the last 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 principal investigator or sub-investigator.

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

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

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

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

- Approximately 10 mL of venous blood will be collected for future research from subjects who consent (if within 21 days after the last vaccination).

9 ASSESSMENT OF SAFETY

9.1 Specification of 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 (hardness)/edema (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, 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.

9.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

9.2.1 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. 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.

AEs, including solicited injection site and systemic (subjective and quantitative) reactions, not meeting the protocol-defined criteria for SAEs will be captured on the appropriate DCF and eCRF. Information to be collected for unsolicited non-serious AEs includes event description, date of onset, licensed study clinician's assessment of severity and relationship to study product and alternate etiology (if not related to study product) (assessed only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the site principal investigator or sub-investigator), date of resolution of the event, seriousness, and outcome. AEs occurring during the trial collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution.

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

AEs must be graded for severity and assessed for relationship to study product (see definitions below). 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 DCF and eCRF.

FDA defines an AE as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

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

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

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 PIMMCs.

Severity of Event: AEs will be assessed by a licensed study clinician listed on the Form FDA 1572 as the site principal investigator or appropriate sub-investigator using a protocol-defined grading system (see Sections 9.2.2 and 9.2.3). 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.

Relationship to Study Product: The licensed study clinician's assessment of an AE's relationship to study product is part of the documentation process, but it 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. The relationship to study product must be assessed for AEs using the terms: related or not related. 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.

9.2.2 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:

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** no pain medication is taken	Subject is aware of pain; there is interference with daily activity **or** it requires repeated use of a non-narcotic pain reliever for >24 hours	Subject is aware of pain, **and** it prevents daily activity or requires any use of a narcotic pain reliever
Tenderness – hurts only when injection site is	The area immediately surrounding the injection	The area immediately surrounding the injection	The area immediately surrounding the injection

Injection Site Reaction	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
touched or the arm is moved	site hurts only when touched or with arm motion, **and** it does **not** interfere with daily activity	site hurts when touched or with arm motion, **and** it interferes with daily activity	site hurts when touched or with arm motion, **and** it prevents daily activity
Pruritus (Itching)	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
Ecchymosis (Bruising)*	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
Erythema (Redness)*	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
Induration (Hardness)/Edema (Swelling)*	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity

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

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

Local (Injection Site) Reactogenicity Measurements

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

* Will not be used as halting criteria.

Subjective Systemic Reactogenicity Grading

Systemic (Subjective)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Feverishness (Chills/Shivering/Sweating)	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)
Fatigue (Tiredness)	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Malaise (General Unwell Feeling)	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Myalgia (Body Aches/Muscular Pain)*	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Arthralgia (Joint Pain)*	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Headache	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
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:

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.

9.2.3 Additional Adverse Event Severity Grading

Pulse and blood pressure[#] will be graded as follows:

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.

For Individuals >65 years of age, pulse and blood pressure[#] will be graded as follows:

Physiologic Parameter	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Bradycardia - bpm	45 – 46	40 – 44	<40
Tachycardia – bpm	101 – 130	131 – 155	>155
Hypotension (systolic) mm Hg	80 – 84	75 – 79	<75
Hypotension (diastolic) mm Hg	50 – 54	45 – 49	<45
Hypertension (systolic) mm Hg	161 – 165	166 – 170	>170
Hypertension (diastolic) mm Hg	96 – 100	101 – 105	>105

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

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

Clinical Safety Laboratory Adverse Event Grading[75]

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.

9.2.4 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 (if not related to study product) by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.
- Recorded on the appropriate SAE form and eCRF.
- Followed through resolution by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.
- Reviewed and evaluated by an Independent Safety Monitor (ISM) (as deemed necessary), the DSMB (periodic review unless related), DMID, and the IRB.

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

The site principal investigator 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.

9.3 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 and 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.

9.3.1 Serious Adverse Events

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

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

In addition to the SAE form, selected SAE data fields must also be entered into AdvantageEDC^{SM}. 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 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.

9.3.2 Regulatory Reporting for Studies Conducted Under DMID-Sponsored IND

Following notification from the site principal investigator or appropriate sub-investigator, DMID, the Investigational New Drug Application (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 principal investigators (i.e., all principal investigators to whom the sponsor is providing drug under its IND(s) or under any principal investigator'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.

9.3.3 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.

9.4 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 and 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 DCF.

9.5 Halting Rules

For the purpose of halting rules only events that occur following the administration of the **AS03 adjuvanted 2017 H7N9** will be considered. 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 an SAE from the time of the first 2017 H7N9 vaccination through 14 days after each 2017 H7N9 vaccination.
- 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 through the subject's last study visit.

This trial will also be halted for DSMB review/recommendation if, within 7 days after administration of any study vaccination, any of the following occurs within the 2017 A/H7N9 IIV AS03-adjuvanted treatment arms (Group 1 or Group 2).

- 7% or more of subjects (with a minimum of 3 subjects) who received at least one dose of study vaccine to date, cumulative to all 2017 H7N9 vaccine administrations, across Groups 1 and 2, experience the same severe (Grade 3) study vaccine-related injection site reaction. Ecchymosis, erythema, and induration (hardness)/edema (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 all 2017 H7N9 vaccine administration, across Groups 1 and 2, 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 all 2017 H7N9 vaccine administration, across Groups 1 and 2, 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 all 2017 H7N9 vaccine administration, across Groups 1 and 2, 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 9.2.2.

Grading scales for clinical safety laboratory AEs are included in Section 9.2.3.

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.

9.6 Safety Oversight

9.6.1 Independent Safety Monitor (ISM)

The ISM is a physician with relevant expertise whose primary responsibility is to provide independent safety monitoring in a timely fashion. **For this trial, an ISM is not required**. However, at each participating VTEU site, and at the request of DMID, in real time, the principal investigator should be able to identify an independent physician to function as an ad hoc ISM. That person should have the privileges to examine the subject, review the subject's medical and study records, and provide an independent medical assessment and recommendation to DMID.

9.6.2 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, solicited and unsolicited AE/SAEs, and 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 review study progress and participant, clinical, safety, and reactogenicity data at the following time points:

- Data review for safety at study specific time frames; at least annually.
- Electronic review when 8-day reactogenicity and clinical safety laboratory data following the first study vaccination is available for 25% of study participants.
- Approximately when 8-day reactogenicity and clinical safety laboratory data following the first study vaccination is available for 75% of study participants.
- 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.
- Ad hoc when a halting rule is met, for immediate concerns regarding observations during this trial, or as needed.

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, including expected and observed rates of the expected AEs. The DSMB will review grouped 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.

The DSMB will operate under the rules of a DMID-approved charter that will be written at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. Procedures for DSMB reviews/meetings will be defined in the charter. The DSMB will review applicable data to include, but not limited to, study progress and participant, clinical, safety and reactogenicity data. Reports may include enrollment and demographic information, medical history, concomitant medications, physical assessments, clinical laboratory values, dosing compliance, solicited and unsolicited AE/SAEs, and HAI and Neut antibody assay results.

DMID or the DSMB chair may convene the DSMB on an ad hoc basis according to protocol criteria or if there are immediate concerns regarding observations during the course of this trial. The DMID Medical Monitor is empowered to stop enrollment and study vaccinations if AEs that meet the halting criteria are reported. The DMID Medical Monitor and the ISM (as deemed necessary) will be responsible for reviewing SAEs in real time. The DSMB will review SAEs on a regular basis and ad hoc during this trial.

10 CLINICAL MONITORING

10.1 Site Monitoring Plan

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

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

11 STATISTICAL CONSIDERATIONS

11.1 Introduction

The goal of this clinical trial is to assess, in healthy adults ages 19 – 64, the safety, reactogenicity, and immunogenicity of a pre-pandemic AS03-adjuvanted 2017 H7N9 IIV when two doses are administered 21 days apart either sequentially or simultaneously (within 15 minutes) with licensed seasonal influenza vaccine. Primary immunogenicity objectives include evaluating interference with response to 2017 H7N9 IIV vaccine virus strain 21 days post dose 2, and evaluating interference with response to seasonal influenza virus strains 21 days post receipt of IIV4.

11.2 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 when 2017 H7N9 IIV is administered sequentially or simultaneously (within 15 minutes) with licensed seasonal influenza 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 11.4.3, along with the probability of observing safety outcomes and the precision of immunogenicity outcomes.

11.3 Study Outcome Measures

Please refer to study outcome measures in Section 3.2.

11.4 Sample Size Considerations

Please refer to study design outlined in Section 4.0.

11.4.1 Study Population

The study population for this clinical trial includes males and non-pregnant females, 19-64 years of age, who are in good health and meet all eligibility criteria. The subjects will be recruited from the general population at the participating VTEU sites that have substantial experience conducting large influenza vaccine studies.

11.4.2 Subject Enrollment and Follow-up

Based on the accrual rates observed in similar studies, it seems reasonable to expect that the participating VTEUs will be able to enroll this trial in a timely fashion. In previous DMID trials of A/H7N9 vaccines, 5 VTEUs recruited 975 healthy adults, ages 19-64 in 10 weeks. Prior experience suggests up to 15% of subjects may be excluded from the per protocol analysis for post dose 3 assessments, either because they did not receive the second or third study vaccinations, were lost-to-follow-up, or because they had a protocol deviation requiring their exclusion from the per protocol analysis.

A total of N=60 in Groups 1-2, and N = 30 in Group 3 will be enrolled and randomized. Assuming up to 15% drop out by Day 64, this will ensure at least N=50 in Groups 1-2 and N=25 in Group 3 are available for the primary immunogenicity analysis.

Follow-up will consist of 2 segments. The first encompasses the core data for this trial and will consist of results for all study visits through approximately 21 days after the last study vaccination. The second segment consists of a 6-month immunogenicity assessment and follow-up safety assessments through approximately 12 months after the last study vaccination.

11.4.3 Sample Size

This study is planned to enroll a minimum of 60 subjects in Groups 1-2, and 30 subjects in Group 3. This 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 and to uncover any safety issues that occur at a sufficiently high rate that they might be observed in a study of this size. As such, the type one error rate, alpha = 0.05, is not adjusted for multiple comparisons.

While this study is not designed to test any specific null hypothesis, the following tables illustrate the precision and power for select estimates and comparisons of interest.

Table 3 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 = 30 or 60), and for all subjects receiving AS03-adjuvanted 2017 H7N9 IIV (N = 120).

Table 3: Power (%) to Detect Safety Events:

Event Frequency	N = 30	N = 60	N = 120
≥10% Very Common	96	>99	>99
≥1%	26	45	70

Common			
≥0.1% Uncommon	3	6	11
≥0.01% Rare	<1	<1	1

Binomial confidence intervals (CI) are widest (have the least precision) when the response rate is 50%. Table 4 is presented to indicate the worst-case scenario for precision of observed exact (Clopper-Pearson) binomial confidence intervals.

Table 4: Precision of Binomial Confidence Intervals:

N	95% CI
30	31-69
60	37-63
120	40-60

For each of the primary immunogenicity objective, a power analysis is provided below for testing the following hypotheses with the planned sample size, where p_c = proportion responders in comparator arm; p_e = proportion responders in experimental arm.

Test for difference in proportion responders:
H_0: $p_c - p_e = 0$ – No difference in proportion responders
H_1: $p_c - p_e \neq 0$ – difference in response rates

Table 5 and Table 6 present the minimum detectable differences in the proportion of subjects responding (e.g., attaining seroconversion or a titer ≥1:40) between two treatment arms using a two-sided Likelihood Ratio Test and alpha = 0.05.

Primary Immunogenicity Objective 1: Evaluate antibody responses against A/H7N9 at approximately 21 days following receipt of two doses of AS03-adjuvanted 2017 H7N9 IIV. Comparison between simultaneous and sequential receipt to IIV4, i.e., Group 1 at Day 43 vs. Group 2 at Day 64.

Table 5: Objective 1 -Minimum Detectable Difference in Proportion Responders with 80% Power (N = 50 per group)

Assumed Proportion Responders comparator arm (p_c)	Minimum detectable difference in response rate ($p_c - p_e$)
0.50	0.27

Assumed Proportion Responders comparator arm (p_c)	Minimum detectable difference in response rate ($p_c - p_e$)
0.60	0.27
0.70	0.27
0.80	0.26
0.90	0.22

Primary Immunogenicity Objective 2: Evaluate antibody responses against the seasonal influenza strains at approximately 21 days following receipt of IIV4.

Comparator Group (N = 75):

- Group 2 (IIV4/H7N9/H7N9) + Group 3 (IIV4) at Day 22

Experimental Groups (N = 50/group):

- Group 1 (H7N9+IIV4/H7N9) at Day 64

Table 6: Objective 2 - Minimum Detectable Difference in Proportion Responders with 80% Power

Assumed Proportion Responders comparator arm (p_c)	Minimum detectable decrease in response rate (p_c - p_e)
0.40	0.23
0.50	0.24
0.60	0.25
0.70	0.25
0.80	0.23
0.90	0.20

11.5 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 9.6.2.

No interim analysis of immunogenicity is planned, however, a preliminary report of safety and immunogenicity data through Day 64 will be prepared as described in Section 11.6; though this report will be released while subjects remain in the trial for long-term safety and immunogenicity 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.

11.5.1 Interim Safety Review

An interim safety review may include enrollment and demographic information, medical history, concomitant medications, physical assessments, clinical laboratory values, 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, including expected and observed rates of the expected AEs. The DSMB will review grouped 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 9.5 are met.

11.5.2 Interim Immunogenicity Review

No interim immunogenicity analysis is planned. Should emergent public health needs dictate immunogenicity review, immune responses will be summarized in terms of strain-specific 2017 A/H7N9 and IIV4 HAI and Neut antibody titers for subjects that receive sequential or simultaneous administration of AS03-adjuvanted 2017 H7N9 IIV and seasonal IIV4. It is anticipated that all analyses will be carried out in parallel for both assays, but reports may be prepared separately for HAI and Neuts if results are available on different timelines. Interim analyses will focus on rates of titers ≥1:40, seroconversion (defined as either a pre-vaccination titer <1:10 and a post-vaccination titer ≥1:40 or a pre-vaccination titer ≥1:10 and a minimum four-fold rise in post-vaccination titer) and GMTs, along with corresponding 95% CIs. No formal hypothesis testing will be included in the interim analysis, and interim results will not have impact on conduct of this trial.

Any immunogenicity reports would be provided by the SDCC to the DMID Scientific Lead and Clinical Project manager, and the DSMB. Reports will include data summarized by treatment arm.

11.6 Final Analysis Plan

Clinical, safety, and reactogenicity data through approximately 21 days after the third study vaccination will represent the primary clinical database for this trial. Once the last subject completes the visit that occurs approximately 21 days after the third study vaccination, the primary clinical database will be cleaned, monitored, and locked. Analyses of safety, reactogenicity, and available immunogenicity (HAI and Neut antibody assays through Day 64) data by treatment arm are planned. A preliminary report will be prepared by the SDCC after the primary clinical database is locked and all HAI and Neut data for the 2017 H7N9 vaccine strain and all IIV4 strains are received through 21 days after the last study vaccination is received. These analyses may be made available to the sponsor for planning subsequent trials and to the lead principal investigator for publication. These analyses will not be used to make any decisions concerning the conduct of this trial. All analyses of data included in the preliminary report 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 laboratories. 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 (SAP) will be developed and finalized prior the primary clinical database lock, which defines the analyses to be included in the Preliminary report, and the final CSR.

11.6.1 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 in Group 2 who discontinue treatment after receiving the single IIV4 dose (Dose 1) but prior to receiving the first dose of the H7N9 vaccine (Dose 2) will be analyzed with group 3. All other 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 or third study vaccination not received,
    - Second or third 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.

11.6.2 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 1-8 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 vs. second, first vs. third, second vs. third, as applicable within each study group) 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 and 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% CIs of AEs in aggregate and by MedDRA® categories will be computed.

Clinical laboratory data will be summarized by severity for each visit and as the maximum over all post-study vaccination visits. Graphical presentations may include box plots.

11.6.3 Immunogenicity Data

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

Immune responses in terms of 2017 H7N9 or IIV4 strain-specific HAI and Neut antibody titers will be summarized by treatment arm at each time point. Analyses will include number and percentage of subjects with a titer ≥1:40, number and percentage of subjects achieving seroconversion (defined as either a pre-vaccination titer <10 and a post-vaccination titer ≥1:40 or a pre-vaccination titer ≥1:10 and a minimum four-fold rise in post-vaccination antibody titer), and GMTs along with corresponding 95% CIs. 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, BMI, and prior receipt of seasonal influenza vaccine(s), and these covariates may be considered statistical modeling. As an exploratory analysis, models may be developed to evaluate the relationship between study vaccination schedule and immune response.

Additionally, N1, N2 and N9 NA-specific antibody assays are in development. If successful, N1, N2 and N9 NA-specific responses may be assessed at baseline, 21, 42, 63, and 180 days after receipt of the first study vaccination. For each time point, summaries may include number

and percentage of subjects with detectable N1, N2 and N9 NA response (to be defined in SAP based following assay development and selection) and GMTs along with corresponding 95% CIs. Descriptive summary statistics will be provided for all assays and time points. The correlation of N1, N2 and 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 N9 NA content of the 2017 H7N9 IIV and the N1 and N2 content of seasonal licensed QIV is planned, and if successful, may be used to correlate the N1, N2 and N9 NA elicited antibody responses to the NA content of the 2017 H7N9 IIV and seasonal IIV4, respectively. Detectable NA antibody responses and GMTs will be summarized stratified by NA content, and statistical modeling may be used to examine the relationship of NA response with NA vaccine content, and study vaccination schedule.

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.

11.6.4 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.

12 DATA COLLECTION FORMS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating VTEU site will maintain appropriate medical and research records for this trial, in compliance with ICH E6, Section 4.9, and regulatory and institutional requirements for the protection of confidentiality of subjects. Each participating VTEU 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, monitoring and evaluation of the study safety and progress. These representatives will be permitted access to all source data, which include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, 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 trial. Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

Interview of subjects is sufficient for obtaining medical history. Solicitation of medical records from the subject's primary care provider is not required.

13 QUALITY CONTROL AND QUALITY ASSURANCE

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

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

14 ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1 Ethical Standard

The site principal investigator will ensure that this trial is conducted in full conformity with principles of the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR 46, 21 CFR 50 and 56, and ICH E6; 62 Federal Regulations 25691 (1997), if applicable. The site principal investigator's institution will hold a current Federalwide Assurance (FWA) issued by the Office of Human Research Protection (OHRP) for federally funded research.

14.2 Institutional Review Board

Prior to enrollment of subjects into this trial, the protocol and ICF will be reviewed and approved by the appropriate IRB listed on its FWA.

The responsible official for the IRB will sign the IRB letter of approval of the protocol prior to the start of this trial and a copy will be provided to DMID. The IRB FWA number will be provided to DMID.

Should amendments to the protocol be required, the amendments will be written by the sponsor and provided to the site principal investigator for submission to the IRB.

14.3 Informed Consent Process

14.3.1 Informed Consent

The site principal investigator will choose subjects in accordance with the eligibility criteria detailed in Section 5.1. Before any study procedures are performed, subjects must sign an ICF that complies with the requirements of 21 CFR Part 50 and 45 CFR 46 and the local IRB. Study personnel may employ IRB-approved recruitment efforts prior to obtaining study consent; however, before any study procedures are performed to determine protocol eligibility an ICF must be signed.

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 subjects will receive a comprehensive explanation of the proposed study

procedures and study interventions/products. This will include the nature, risks and possible benefits of this trial, alternate therapies, any known AEs, the investigational status of the study interventions/products, and the other elements that are part of obtaining proper informed consent. Subjects will also receive a detailed explanation of the proposed use and disclosure of their protected health information, including specifically their serum samples. Subjects will be allowed sufficient time to consider participation in this research trial, after having the nature, risks, and possible benefits of this trial explained to them, 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 describing in detail the study interventions/products, study procedures, risks, and possible benefits will be given to subjects. The ICF must not include any exculpatory statements. ICFs will be IRB-approved and subjects will be asked to read and review the appropriate document. Upon reviewing the appropriate document, the site principal investigator (or designee) will explain this research trial to subjects and answer any questions that may arise. Subjects must sign the ICF, and written documentation of the informed consent process is required prior to starting any study procedures being done specifically for this trial, including determining eligibility and administering study product.

By signing the ICF, subjects agree to complete all study procedures required by this trial, unless the subject withdraws voluntarily, or is withdrawn or terminated from this trial for any reason. The rights and welfare of subjects will be protected by emphasizing to subjects that the quality of their medical care will not be adversely affected if they decline to participate in or withdraw from this trial.

DMID will provide the site principal investigator, in writing, any new information that significantly impacts the subject's risk of receiving the investigational products. This 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.

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

This trial will be inclusive of all subjects ages 19-64 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. Adults aged 18 are excluded because the CDC-recommended adult immunization schedule considers adults as age 19 and above, and therefore this is the subject population chosen for this study [80]. 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 AS03 adjuvant poses any risks to an unborn child. As of November 22, 2015 (per the most current version of the manufacturer's IB), the available data for women who become pregnant during clinical trials of AS03-adjuvanted (pre) pandemic influenza vaccines do not suggest any causal relationship between adverse pregnancy outcomes and receipt of an AS03-adjuvanted vaccine. Women of childbearing potential who are 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 who are not postmenopausal for ≥1 year must use an acceptable contraception method that may include, but is not limited to, non-male sexual relationships, abstinence from sexual intercourse with a male partner, monogamous relationship with a vasectomized partner who has been vasectomized for at least 180 days prior to the subject receiving the first study vaccination, barrier methods such as condoms or diaphragms with spermicide or foam, , effective intrauterine devices, NuvaRing® and licensed hormonal methods, such as implants, injectables, or oral contraceptives ("the pill") 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.

14.5 Subject Confidentiality

Subject confidentiality is strictly held in trust by the site principal investigators, other study personnel, the sponsor, and their agents. This confidentiality is extended to cover testing of biological samples, in addition to the clinical information relating to participating subjects. Subjects will have code numbers and will not be identified by name.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning this trial or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All information provided by the sponsor and all data and information generated by the participating VTEU sites as part of this trial (other than a subject's medical records) will be kept

confidential by the site principal investigators and other study personnel to the extent permitted by law. These restrictions do not apply to: (1) information which becomes publicly available through no fault of the site principal investigators or other study personnel; (2) information which is necessary to disclose in confidence to an IRB solely for the evaluation of this trial; (3) information which is necessary to disclose in order to provide appropriate medical care to a study subject; or (4) study results which may be published as described in Section 17.

The study monitor, applicable regulatory authorities, such as the FDA, or other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the site principal investigators. This includes, but is not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this trial. The participating VTEU sites will permit access to such records.

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

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

14.6 Study Discontinuation

If this trial is discontinued, subjects, who have signed the ICF and are randomized and vaccinated, will continue to be followed for safety for the duration of the prescribed safety follow-up period. No further study vaccinations will be administered.

14.7 Costs, Subject Compensation, and Research Related Injuries

There is no cost to subjects for taking part in this trial.

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 participating VTEU site and the site principal investigator that an injury occurred to a subject as a direct result of the tests or treatments that are done for this trial, then referrals to appropriate health care facilities will be provided to the subject. Study personnel will try to reduce, control, and treat any complications from this trial. Immediate medical treatment may be provided by the participating VTEU site, such as giving emergency medications to stop immediate allergic reactions to the study vaccine. No financial compensation will be provided to the subject by the participating VTEU 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 Sanofi Pasteur and adjuvant (AS03) manufactured by GSK), are covered under the Public Readiness and Emergency Preparedness Act (PREP Act), as described in Section 2.1.1.

14.8 Future Use of Stored Specimens

Residual samples/specimens are those that are left over after the study has been completed. Subjects may be asked for permission to keep any remaining (residual) clinical samples (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 the retention of those samples for possible future use 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 for purposes other than per protocol analysis with investigators at the participating VTEU site and with other investigators at other institutions once the clinical study report has been finalized.

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 form allows the option to choose that option. It is anticipated that up to ten 0.5 mL aliquots of serum from

each extra 10 mL venous blood sample 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 research clinical samples will be stored indefinitely at a central clinical storage facility.

Unlike residual samples, samples/specimens collected during the study solely for the purpose of future research may be requested from DMID and shipped from the DMID CMS at any time.

The samples (residual and the extra venous blood sample collected solely for future use) will not be sold or used directly for production of any commercial product. No genetic tests will be performed on samples. Each sample will be encoded (labeled) only with a barcode and a unique tracking number to protect subject confidentiality.

There are no benefits to subjects in the collection, storage and subsequent use of their specimens for future research. Reports about future research done with subjects' samples will NOT be kept in their health records.

Subjects who are provided the option to decide if residual samples may be retained for possible future use or if other blood specimens may be collected specifically for future use may change those decisions at any time by notifying the study doctors or nurses in writing. However, if the subject originally consents to future use of residual samples or collection of samples specifically for future research, and subsequently changes his/her decision, any data from a previously collected sample may still be used for this research.

15 DATA HANDLING AND RECORD KEEPING

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

DCFs will be derived from the eCRF and provided by the SDCC to record and maintain data for each subject enrolled in this trial. All DCFs should be completed in a neat, legible manner to ensure accurate interpretation of data. Black or blue 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.

Data reported in the eCRF derived from the DCFs should be consistent with the DCFs or the discrepancies should be explained.

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

15.1 Data Management Responsibilities

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

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

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

15.2 Data Capture Methods

Clinical (including, but not limited to, AE/SAEs, concomitant medications, medical history, physical assessments, and clinical laboratory values), reactogenicity and immunogenicity data will be entered into a 21 CFR 11-compliant Internet Data Entry System provided by the SDCC. The data system includes password protection and internal quality checks, such as automatic

range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical and reactogenicity data will be entered directly from the DCFs completed by the study personnel.

15.3 Types of Data

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

15.4 Timing/Reports

Clinical, safety and reactogenicity data through approximately 21 days after the second adjuvanted H7N9 study vaccination for Groups 1 and 2 will represent the primary clinical database for this trial. Once the last subject completes the visit that occurs approximately 21 days after the last adjuvanted H7N9 study vaccination, the primary clinical database will be cleaned, monitored and locked. Analyses of safety, reactogenicity, and primary and secondary immunogenicity data by treatment are planned. A preliminary report will be prepared by the SDCC after the primary clinical database is locked and all HAI and Neut data through 21 days after the last study vaccination are received. These analyses may be made available to the sponsor for planning subsequent trials and to the lead principal investigator for publication. These analyses will not be used to make any decisions concerning the conduct of this trial. All analyses of data included in the preliminary report for early release will be considered the final analysis of these data, and also included in the final CSR.

Analysis of exploratory immunogenicity endpoints may be performed and released as the data is available from the central clinical 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.

Additional statistical reports may be generated as deemed necessary and appropriate by DMID. Safety and immunogenicity summary reports may be generated for the DSMB.

After the final CSR is complete, and upon request and DMID approval, the SDCC will provide the participating VTEU sites with a summary of results by treatment arm and/or subject treatment assignments. In this regard, the participating VTEU sites requesting such information to share with study subjects must do so in compliance with their respective IRB guidelines.

15.5 Study Records Retention

Study records and reports including, but not limited to, eCRFs, source documents, ICFs, and study drug disposition records shall be maintained for 2 years after a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for the drug, until 2 years after the investigation is discontinued and the FDA has been notified. ICFs for future use will be maintained as long as the sample exists.

The participating VTEU sites must contact DMID for authorization prior to the destruction of any study records.

16 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the study protocol, GCP, or protocol-specific MOP requirements. The noncompliance may be either on the part of the subject, the site principal investigator, or other study 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 principal investigator and other study personnel to use continuous vigilance to identify and report deviations within five working days of identification of the protocol deviation, or within five working days of the scheduled protocol-required activity. All deviations must be promptly reported to DMID, via the SDCC's AdvantageEDC^{SM}.

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

17 PUBLICATION POLICY

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 does not plan to request certification of delayed posting.

Refer to:

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

18 LITERATURE REFERENCES

1. Centers for Disease, C. and Prevention, *Emergence of avian influenza A(H7N9) virus causing severe human illness - China, February-April 2013.* MMWR Morb Mortal Wkly Rep, 2013. **62**(18): p. 366-71.
2. Fouchier, R.A., et al., *Avian influenza A virus (H7N7) associated with human conjunctivitis and a fatal case of acute respiratory distress syndrome.* Proc Natl Acad Sci U S A, 2004. **101**(5): p. 1356-61.
3. Lindstrom, S., et al., *Human infections with novel reassortant influenza A(H3N2)v viruses, United States, 2011.* Emerg Infect Dis, 2012. **18**(5): p. 834-7.
4. Peiris, M., et al., *Human infection with influenza H9N2.* Lancet, 1999. **354**(9182): p. 916-7.
5. Perez-Padilla, R., et al., *Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico.* N Engl J Med, 2009. **361**(7): p. 680-9.
6. Subbarao, K., et al., *Characterization of an avian influenza A (H5N1) virus isolated from a child with a fatal respiratory illness.* Science, 1998. **279**(5349): p. 393-6.
7. Oxford, J.S., *Influenza A pandemics of the 20th century with special reference to 1918: virology, pathology and epidemiology.* Rev Med Virol, 2000. **10**(2): p. 119-33.
8. Patriarca, P.A. and N.J. Cox, *Influenza pandemic preparedness plan for the United States.* J Infect Dis, 1997. **176 Suppl 1**: p. S4-7.
9. Galasso, G.J., F.J. Tyeryar, Jr., and J.R. La Montagne, *Overview of clinical trials of influenza vaccines, 1976.* J Infect Dis, 1977. **136 Suppl**: p. S425-8.
10. La Montagne, J.R., et al., *Summary of clinical trials of inactivated influenza vaccine - 1978.* Rev Infect Dis, 1983. **5**(4): p. 723-36.
11. Couch, R.B. and J.A. Kasel, *Immunity to influenza in man.* Annu Rev Microbiol, 1983. **37**: p. 529-49.
12. Couch, R.B., et al., *Antibody correlates and predictors of immunity to naturally occurring influenza in humans and the importance of antibody to the neuraminidase.* J Infect Dis, 2013. **207**(6): p. 974-81.
13. Memoli, M.J., et al., *Evaluation of Antihemagglutinin and Antineuraminidase Antibodies as Correlates of Protection in an Influenza A/H1N1 Virus Healthy Human Challenge Model.* MBio, 2016. **7**(2): p. e00417-16.
14. Ennis, F.A., et al., *Correlation of laboratory studies with clinical responses to A/New Jersey influenza vaccines.* J Infect Dis, 1977. **136 Suppl**: p. S397-406.
15. Gross, P.A., et al., *Immunization of elderly people with high doses of influenza vaccine.* J Am Geriatr Soc, 1988. **36**(3): p. 209-12.
16. Keitel, W.A., et al., *High doses of purified influenza A virus hemagglutinin significantly augment serum and nasal secretion antibody responses in healthy young adults.* J Clin Microbiol, 1994. **32**(10): p. 2468-73.
17. Matzkin, H. and E. Nili, *Accidental tenfold overdose of influenza vaccine: a clinical and serological study.* Isr J Med Sci, 1984. **20**(5): p. 411-5.

18. Mostow, S.R., et al., *Inactivated vaccines. 1. Volunteer studies with very high doses of influenza vaccine purified by zonal ultracentrifugation.* Postgrad Med J, 1973. **49**(569): p. 152-8.
19. Palache, A.M., et al., *Antibody response after influenza immunization with various vaccine doses: a double-blind, placebo-controlled, multi-centre, dose-response study in elderly nursing-home residents and young volunteers.* Vaccine, 1993. **11**(1): p. 3-9.
20. Remarque, E.J., et al., *Improvement of the immunoglobulin subclass response to influenza vaccine in elderly nursing-home residents by the use of high-dose vaccines.* Vaccine, 1993. **11**(6): p. 649-54.
21. Ruben, F.L. and G.G. Jackson, *A new subunit influenza vaccine: acceptability compared with standard vaccines and effect of dose on antigenicity.* J Infect Dis, 1972. **125**(6): p. 656-64.
22. Ruben, F.L., C.W. Potter, and C.H. Stuart-Harris, *Humoral and secretory antibody responses to immunization with low and high dosage split influenza virus vaccine.* Arch Virol, 1975. **47**(2): p. 157-66.
23. Keitel, W.A., et al., *Increasing doses of purified influenza virus hemagglutinin and subvirion vaccines enhance antibody responses in the elderly.* Clin Diagn Lab Immunol, 1996. **3**(5): p. 507-10.
24. Couch, R.B., et al., *A randomized clinical trial of an inactivated avian influenza A (H7N7) vaccine.* PLoS One, 2012. **7**(12): p. e49704.
25. Treanor, J.J., et al., *Safety and immunogenicity of an inactivated subvirion influenza A (H5N1) vaccine.* N Engl J Med, 2006. **354**(13): p. 1343-51.
26. Atmar, R.L. and W.A. Keitel, *Adjuvants for pandemic influenza vaccines.* Curr Top Microbiol Immunol, 2009. **333**: p. 323-44.
27. Bresson, J.L., et al., *Safety and immunogenicity of an inactivated split-virion influenza A/Vietnam/1194/2004 (H5N1) vaccine: phase I randomised trial.* Lancet, 2006. **367**(9523): p. 1657-64.
28. Keitel, W.A., et al., *Safety and immunogenicity of an inactivated influenza A/H5N1 vaccine given with or without aluminum hydroxide to healthy adults: results of a phase I-II randomized clinical trial.* J Infect Dis, 2008. **198**(9): p. 1309-16.
29. Carmona, A., et al., *Immunogenicity and safety of AS03-adjuvanted 2009 influenza A H1N1 vaccine in children 6-35 months.* Vaccine, 2010. **28**(36): p. 5837-44.
30. Diez-Domingo, J., et al., *Immunogenicity and Safety of H5N1 A/Vietnam/1194/2004 (Clade 1) AS03-adjuvanted prepandemic candidate influenza vaccines in children aged 3 to 9 years: a phase ii, randomized, open, controlled study.* Pediatr Infect Dis J, 2010. **29**(6): p. e35-46.
31. Leroux-Roels, I., et al., *Antigen sparing and cross-reactive immunity with an adjuvanted rH5N1 prototype pandemic influenza vaccine: a randomised controlled trial.* Lancet, 2007. **370**(9587): p. 580-9.
32. McElhaney, J.E., et al., *AS03-adjuvanted versus non-adjuvanted inactivated trivalent influenza vaccine against seasonal influenza in elderly people: a phase 3 randomised trial.* Lancet Infect Dis, 2013. **13**(6): p. 485-96.
33. Vogel, F.R., et al., *Emulsion-based adjuvants for influenza vaccines.* Expert Rev Vaccines, 2009. **8**(4): p. 483-92.

34. *Increased risk of narcolepsy observed also among adults vaccinated with Pandemrix in Finland* National Narcolepsy Task Force. National Institute for Health and Welfare (THL) Finland.
35. *A registry based comparative cohort study in four Swedish counties of the risk for narcolepsy after vaccination with Pandemrix – a first and preliminary report.*
36. Choe, Y.J., G.R. Bae, and D.H. Lee, *No association between influenza A(H1N1)pdm09 vaccination and narcolepsy in South Korea: an ecological study.* Vaccine, 2012. **30**(52): p. 7439-42.
37. Dauvilliers, Y., et al., *Increased risk of narcolepsy in children and adults after pandemic H1N1 vaccination in France.* Brain, 2013. **136**(Pt 8): p. 2486-96.
38. Eurosurveillance editorial, t., *Swedish Medical Products Agency publishes report from a case inventory study on Pandemrix vaccination and development of narcolepsy with cataplexy.* Euro Surveill, 2011. **16**(26).
39. Miller, E., et al., *Risk of narcolepsy in children and young people receiving AS03 adjuvanted pandemic A/H1N1 2009 influenza vaccine: retrospective analysis.* BMJ, 2013. **346**: p. f794.
40. Montplaisir, J., et al., *Risk of narcolepsy associated with inactivated adjuvanted (AS03) A/H1N1 (2009) pandemic influenza vaccine in Quebec.* PLoS One, 2014. **9**(9): p. e108489.
41. Nohynek, H., et al., *AS03 adjuvanted AH1N1 vaccine associated with an abrupt increase in the incidence of childhood narcolepsy in Finland.* PLoS One, 2012. **7**(3): p. e33536.
42. O'Flanagan, D., et al., *Investigation of an association between onset of narcolepsy and vaccination with pandemic influenza vaccine, Ireland April 2009-December 2010.* Euro Surveill, 2014. **19**(17): p. 15-25.
43. Wijnans, L., et al., *The incidence of narcolepsy in Europe: before, during, and after the influenza A(H1N1)pdm09 pandemic and vaccination campaigns.* Vaccine, 2013. **31**(8): p. 1246-54.
44. *A Phase II Randomized, Partially-Blinded, Controlled, Trial in Healthy Adults Aged 65 Years and Older to Assess the Safety, Reactogenicity, and Immunogenicity of an MF59-Adjuvanted, Monovalent Inactivated Influenza A/H7N9 Virus Vaccine Administered Intramuscularly at Different Intervals and Dosages.*
45. Chen, W.H., et al., *Safety, Reactogenicity, and Immunogenicity of Inactivated Monovalent Influenza A(H5N1) Virus Vaccine Administered With or Without AS03 Adjuvant.* Open Forum Infect Dis, 2014. **1**(3): p. ofu091.
46. Jackson, L.A., et al., *Effect of Varying Doses of a Monovalent H7N9 Influenza Vaccine With and Without AS03 and MF59 Adjuvants on Immune Response: A Randomized Clinical Trial.* JAMA, 2015. **314**(3): p. 237-46.
47. Jackson, L.A., et al., *Immunogenicity and safety of varying dosages of a monovalent 2009 H1N1 influenza vaccine given with and without AS03 adjuvant system in healthy adults and older persons.* J Infect Dis, 2012. **206**(6): p. 811-20.
48. Mulligan, M.J., et al., *Point-of-Use Mixing of Influenza H5N1 Vaccine and MF59 Adjuvant for Pandemic Vaccination Preparedness: Antibody Responses and Safety. A Phase 1 Clinical Trial.* Open Forum Infect Dis, 2014. **1**(3): p. ofu102.

49. Mulligan, M.J., et al., *Serological responses to an avian influenza A/H7N9 vaccine mixed at the point-of-use with MF59 adjuvant: a randomized clinical trial.* JAMA, 2014. **312**(14): p. 1409-19.
50. Lee, Y.J., et al., *Novel reassortant influenza A(H5N8) viruses, South Korea, 2014.* Emerg Infect Dis, 2014. **20**(6): p. 1087-9.
51. Wu, H., et al., *Novel reassortant influenza A(H5N8) viruses in domestic ducks, eastern China.* Emerg Infect Dis, 2014. **20**(8): p. 1315-8.
52. Gao, R., et al., *Human infection with a novel avian-origin influenza A (H7N9) virus.* N Engl J Med, 2013. **368**(20): p. 1888-97.
53. *Analysis of recent scientific information on avian influenza A(H7N9) virus.* WHO Influenza Update, 2017.
54. *Human infection with avian influenza A(H7N9) virus – China: 07 December 2017.* WHO Emergencies preparedness, response, 2017.
55. *WHO Emergencies preparedness, response- Disease Outbreak News 5 April 2017.*
56. Zhou, J., et al., *Biological features of novel avian influenza A (H7N9) virus.* Nature, 2013. **499**(7459): p. 500-3.
57. Zhu, H., et al., *Infectivity, transmission, and pathology of human-isolated H7N9 influenza virus in ferrets and pigs.* Science, 2013. **341**(6142): p. 183-6.
58. Li, Y., et al., *Evolving HA and PB2 genes of influenza A (H7N9) viruses in the fifth wave - Increasing threat to both birds and humans?* J Infect, 2017.
59. Hoskins, T.W., et al., *Controlled trial of inactivated influenza vaccine containing the a-Hong Kong strain during an outbreak of influenza due to the a-England-42-72 strain.* Lancet, 1973. **2**(7821): p. 116-20.
60. Hoskins, T.W., et al., *Influenza at Christ's Hospital: March, 1974.* Lancet, 1976. **1**(7951): p. 105-8.
61. Belongia, E.A., et al., *Repeated annual influenza vaccination and vaccine effectiveness: review of evidence.* Expert Rev Vaccines, 2017. **16**(7): p. 1-14.
62. Keitel, W.A., et al., *Efficacy of repeated annual immunization with inactivated influenza virus vaccines over a five year period.* Vaccine, 1997. **15**(10): p. 1114-22.
63. Ohmit, S.E., et al., *Influenza vaccine effectiveness in the community and the household.* Clin Infect Dis, 2013. **56**(10): p. 1363-9.
64. Langley, J.M., et al., *A randomized, controlled non-inferiority trial comparing A(H1N1)pmd09 vaccine antigen, with and without AS03 adjuvant system, co-administered or sequentially administered with an inactivated trivalent seasonal influenza vaccine.* BMC Infect Dis, 2012. **12**: p. 279.
65. Peeters, M., et al., *Safety and immunogenicity of an AS03-adjuvanted A(H1N1)pmd09 vaccine administered simultaneously or sequentially with a seasonal trivalent vaccine in adults 61 years or older: data from two multicentre randomised trials.* Vaccine, 2012. **30**(45): p. 6483-91.
66. Roy-Ghanta, S., et al., *Responses to A(H1N1)pdm09 influenza vaccines in participants previously vaccinated with seasonal influenza vaccine: a randomized, observer-blind, controlled study.* J Infect Dis, 2014. **210**(9): p. 1419-30.
67. Uno, S., et al., *Effect of prior vaccination with a seasonal trivalent influenza vaccine on the antibody response to the influenza pandemic H1N1 2009 vaccine: a randomized controlled trial.* Microbiol Immunol, 2011. **55**(11): p. 783-9.

68. Chen, W.H., et al., *Phase 2 assessment of the safety and immunogenicity of two inactivated pandemic monovalent H1N1 vaccines in adults as a component of the U.S. pandemic preparedness plan in 2009.* Vaccine, 2012. **30**(28): p. 4240-8.
69. Vajo, Z., et al., *Safety and immunogenicity of a 2009 pandemic influenza A H1N1 vaccine when administered alone or simultaneously with the seasonal influenza vaccine for the 2009-10 influenza season: a multicentre, randomised controlled trial.* Lancet, 2010. **375**(9708): p. 49-55.
70. Madan, A., et al., *Immunogenicity and Safety of an AS03-Adjuvanted H7N9 Pandemic Influenza Vaccine in a Randomized Trial in Healthy Adults.* J Infect Dis, 2016. **214**(11): p. 1717-1727.
71. Lasky, T., et al., *The Guillain-Barre syndrome and the 1992-1993 and 1993-1994 influenza vaccines.* N Engl J Med, 1998. **339**(25): p. 1797-802.
72. Haber, P., et al., *Guillain-Barre syndrome following influenza vaccination.* JAMA, 2004. **292**(20): p. 2478-81.
73. De Wals, P., et al., *Risk of Guillain-Barre syndrome following H1N1 influenza vaccination in Quebec.* JAMA, 2012. **308**(2): p. 175-81.
74. Juurlink, D.N., et al., *Guillain-Barre syndrome after influenza vaccination in adults: a population-based study.* Arch Intern Med, 2006. **166**(20): p. 2217-21.
75. Salmon, D.A., et al., *Association between Guillain-Barre syndrome and influenza A (H1N1) 2009 monovalent inactivated vaccines in the USA: a meta-analysis.* Lancet, 2013. **381**(9876): p. 1461-8.
76. Wise, M.E., et al., *Guillain-Barre syndrome during the 2009-2010 H1N1 influenza vaccination campaign: population-based surveillance among 45 million Americans.* Am J Epidemiol, 2012. **175**(11): p. 1110-9.
77. Polakowski, L.L., et al., *Chart-confirmed guillain-barre syndrome after 2009 H1N1 influenza vaccination among the Medicare population, 2009-2010.* Am J Epidemiol, 2013. **178**(6): p. 962-73.
78. Dodd, C.N., et al., *International collaboration to assess the risk of Guillain Barre Syndrome following Influenza A (H1N1) 2009 monovalent vaccines.* Vaccine, 2013. **31**(40): p. 4448-58.
79. Sullivan, S.S., *Narcolepsy in adolescents.* Adolesc Med State Art Rev, 2010. **21**(3): p. 542-55, x-xi.
80. CDC, *Recommended Immunizations for Adults: By Age.* 2017.

APPENDICES

APPENDIX A: SCHEDULE OF STUDY PROCEDURES AND EVALUATIONS

Study Schedule, Group 1: Vaccination Period

Study Visit Number	**V00**	**V01**	**V02**	**V03**	**V04[ψ]**	**V05**	**V06**
Study Day post Dose 1	**Screening (Optional) D -28 to -1**	**Enrollment Dose 1 D1**	**D4[±1]**	**D8[+2]**	**D22[+7]**	**D25**	**D29**
Study Day post Dose 2					**Dose 2 D1**	**D4[±1]**	**D8[+2]**
Obtain Informed Consent∞	X	X¬					
Collect Demographic Information	X	X†*					
Review Eligibility Criteria	X	X†¬[1]			X†		
Medical History@	X	X†¬*		X	X		X
Concomitant Medications	X[ς]	X†¬[ς]	X[ς]	X[ς]	X[ς]	X[ς]	X[ς]
Vital Signs$ (Oral Temperature%, Pulse, and BP)	X	X†			X†[2]		
Height and Weight	X	X†*					
Physical Examination[3]	X	{X}†*		{X}	{X}		{X}
Urine or Serum Pregnancy Test	X^	X†^			X†^		
Venous Blood Collection for ESR	X	X≠*					
Venous Blood Collection for Clinical Safety Laboratory Evaluations~		X†		X	X†		X
Venous Blood Collection for Immunogenicity Assays		X†			X†		
Serum Sample Collected for Future Research[4]		X†		X	X†		X
Safety Follow-up Phone Call			X			X	

Study Visit Number	**V00**	**V01**	**V02**	**V03**	**V04[ψ]**	**V05**	**V06**
Study Day post Dose 1	**Screening (Optional) D -28 to -1**	**Enrollment Dose 1 D1**	**D4[±1]**	**D8[+2]**	**D22[+7]**	**D25**	**D29**
Study Day post Dose 2					**Dose 2 D1**	**D4[±1]**	**D8[+2]**
Enrollment in AdvantageEDC[SM] and Randomization		X[†]					
Pre-Administration Reactogenicity Assessments		X[†]			X		
Vaccination		X			X		
20-minute Evaluation After Study Vaccination		X			X		
Examine Study Vaccination Site		X		X	X		X
Post-Administration Reactogenicity Assessments		X			X		
Distribute Memory Aid and Study-Related Materials		X			X		
Review Memory Aid			X	X		X	X
AE/SAE Assessment		X[&]	X[&]	X[&]	X[&]	X[&]	X[&]

∞ Prior to study procedures.
† Prior to study vaccination.
[1] Review results of clinical screening (ESR) or 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 screening (optional) or on Day 1 prior to the first study vaccination and interim medical history will be obtained by interview of subjects at follow-up visits after Dose 1
ς Receipt of non-study influenza vaccines will be solicited through approximately 180 days after the last study vaccination, and reported in the eCRF.
* Not required if done at the optional screening visit.
√ All current medications and medications taken within 60 days prior to signing the ICF.
$ 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 third 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, and nervous system.
{} Targeted physical examination if indicated based on review of interim medical history.
^ May be performed on all women of childbearing potential at screening (optional) and will be performed within 24 hours prior to each vaccination and results must be negative and known prior to each study vaccination.

≠ To be performed locally by the site. The ESR value must be confirmed as <30 mm/hr prior to randomization and first study vaccination.
~ Includes WBC, Hgb, PLT, ALT, T. Bili, Cr.
Ψ Subjects who do not receive the third 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 immunogenicity assays at approximately 21 and 180 days after their first study vaccination.
4 For subjects who have consented to collected of serum for future research.
& Inclusive of reactogenicity assessments performed on the day of each vaccination through 7 days after each study vaccination.

Study Schedule, Group 1: Follow-up Period

Study Visit Number	**V07**	**V08**	**V09Ψ**	**V10**	**V11**	Early Termination (if needed)	Unscheduled (if needed)
Study Day post Dose 1	**D43**	**D64**	**D181 [±14]**	**D202**	**D387**		
Study Day post Dose 2	**D22[+7]**	**D43[+7]**		**D181[±14]**	**D366[±14]**		
Medical History@	X	X	X	X		X	X (if indicated)
Concomitant Medications	X§	X§	X§	X§		X (if within 21 days after last study vaccination and receipt of any non-study influenza vaccine will be recorded if within 180 days after the 2nd study vaccination)	X (if within 21 days after last study vaccination and receipt of any non-study influenza vaccine will be recorded if within 180 days after the 2nd study vaccination)
Vital Signs$ (Oral Temperature%, Pulse, and BP)						X (may be obtained if indicated)	X (may be obtained if indicated)
Physical Examination[3]	{X}	{X}	{X}	{X}		{X}	{X}
Venous Blood Collection for Clinical Safety Laboratory Evaluations~						X (if within 7 days after the last study vaccination)	X (if indicated)
Venous Blood Collection for Immunogenicity Assays	X		X	X		X(if within 21 days after last study vaccination	X(if within 21 days after last study vaccination
Serum Sample Collected for Future Research[4]	X	X	X	X		X(if within 21 days after last study vaccination	X(if within 21 days after last study vaccination

Safety Follow-up Phone Call					X		
Examine Study Vaccination Site						X (if within 7 days after last study vaccination)	X (if within 7 days after last study vaccination)
Post-Administration Reactogenicity Assessments						X (if within 7 days after last study vaccination)	X (if within 7 days after last study vaccination)
Review Memory Aid						X (if within 7 days after last study vaccination)	X (if within 7 days after last study vaccination)
AE/SAE Assessment	X	X	X	X	X	X[&]	X[&]

[@] Complete medical history will be obtained by interview of subjects at screening (optional) or on Day 1 prior to the first study vaccination and interim medical history will be obtained by interview of subjects at follow-up visits after Dose 1
[ς] Receipt of non-study influenza vaccines will be solicited through approximately 180 days after the last study vaccination, and reported in the eCRF.
[$] 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.
{} Targeted physical examination if indicated based on review of interim medical history
.~ Includes WBC, Hgb, PLT, ALT, T. Bili, Cr.
[Ψ] Subjects who do not receive the third 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 immunogenicity assays at approximately 21 and 180 days after their first study vaccination.
[4] For subjects who have consented to collected of serum for future use.

Study Schedule, Group 2: Vaccination Period

Study Visit Number	**V00**	**V01**	**V02**	**V03**	**V04[Ψ]**	**V05**	**V06**	**V07[Ψ]**	**V08**
Study Day post Dose 1	**Screening (Optional) D -28 to -1**	**Enrollment Dose 1 D1**	**D4[±1]**	**D8[+2]**	**D22[+7]**	**D25**	**D29**	**D43**	**D46**
Study Day post Dose 2					**Dose 2 D1**	**D4[±1]**	**D8[+2]**	**D22[+7]**	**D25**
Study Day post Dose 3								**Dose 3 D1**	**D4[±1]**
Study Procedure/Evaluation									
Obtain Informed Consent∞	X	X¬							
Collect Demographic Information	X	X[†*]							
Review Eligibility Criteria	X	X[†¬ı]			X[†]			X[†]	
Medical History[@]	X	X[†¬*]		X	X		X	X	

Study Visit Number	**V00**	**V01**	**V02**	**V03**	**V04ᵠ**	**V05**	**V06**	**V07ᵠ**	**V08**
Study Day post Dose 1	**Screening (Optional) D -28 to -1**	**Enrollment Dose 1 D1**	**D4[±1]**	**D8[+2]**	**D22[+7]**	**D25**	**D29**	**D43**	**D46**
Study Day post Dose 2					**Dose 2 D1**	**D4[±1]**	**D8[+2]**	**D22[+7]**	**D25**
Study Day post Dose 3								**Dose 3 D1**	**D4[±1]**
Study Procedure/Evaluation									
Concomitant Medications	Xᶲ	X†¬ᶲ	Xᶲ	Xᶲ	Xᶲ	Xᶲ	Xᶲ	Xᶲ	Xᶲ
Vital Signs$ (Oral Temperature%, Pulse, and BP)	X	X†			X†2			X†2	
Height and Weight	X	X†*							
Physical Examination[3]	X	X†*		{X}	{X}		{X}	{X}	
Urine or Serum Pregnancy Test	X^	X†^			X†^			X†^	
Venous Blood Collection for ESR	X	X≠*							
Venous Blood Collection for Clinical Safety Laboratory Evaluations~		X†		X	X†		X	X†	
Venous Blood Collection for Immunogenicity Assays		X†			X†			X†	
Serum Sample Collected for Future Research[4]		X†		X	X†		X	X†	
Safety Follow-up Phone Call			X			X			X
Enrollment in AdvantageEDC[SM] and Randomization		X†							
Pre-Administration Reactogenicity Assessments		X†			X			X	
Vaccination		X			X			X	
20-minute Evaluation After Vaccination		X			X			X	
Examine Vaccination Site		X		X	X		X	X	

Study Visit Number	**V00**	**V01**	**V02**	**V03**	**V04$^{\Psi}$**	**V05**	**V06**	**V07$^{\Psi}$**	**V08**
Study Day post Dose 1	**Screening (Optional) D -28 to -1**	**Enrollment Dose 1 D1**	**D4[±1]**	**D8[+2]**	**D22[+7]**	**D25**	**D29**	**D43**	**D46**
Study Day post Dose 2					**Dose 2 D1**	**D4[±1]**	**D8[+2]**	**D22[+7]**	**D25**
Study Day post Dose 3								**Dose 3 D1**	**D4[±1]**
Study Procedure/Evaluation									
Post-Administration Reactogenicity Assessments		X			X			X	
Distribute Memory Aid and Study-Related Materials		X			X			X	
Review Memory Aid			X	X		X	X		X
AE/SAE Assessment		X[&]	X[&]	X[&]	X[&]	X[&]	X[&]	X[&]	X[&]

∞ Prior to study procedures.
† Prior to study vaccination.
[1] Review results of clinical screening (ESR) or 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 screening (optional) or on Day 1 prior to the first study vaccination and interim medical history will be obtained by interview of subjects at follow-up visits after the first study vaccination.
ς Receipt of non-study influenza vaccines will be solicited through approximately 180 days after the last study vaccination, and reported in the eCRF.
* Not required if done at the optional screening visit.
√ All current medications and medications taken within 60 days prior to signing the ICF.
$ 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 third 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, and nervous system.
{} Targeted physical examination if indicated based on review of interim medical history.
^ May be performed on all women of childbearing potential at screening (optional) and will be performed within 24 hours prior to each vaccination and results must be negative and known prior to each study vaccination.
≠ To be performed locally by the site. The ESR value must be confirmed as <30 mm/hr prior to randomization and first study vaccination.
~ Includes WBC, Hgb, PLT, ALT, T. Bili, Cr.
Ψ Subjects who do not receive the third 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 immunogenicity assays at approximately 21 and 180 days after their first study vaccination.
[4] For subjects who have consented to collected of serum for future use.
& Inclusive of reactogenicity assessments performed on the day of each vaccination through 7 days after each study vaccination.

Study Schedule, Group 2: Follow-up Period

Study Visit Number	**V09**	**V10**	**V11ψ**	**V12**	**V13**	Early Termination (if needed)	Unscheduled (if needed)
Study Day post Dose 1	**D50**	**D64**	**D181 [±14]**	**D223**	**D408**		
Study Day post Dose 2	**D29**	**D43**		**D202**	**D387**		
Study Day post Dose 3	**D8[+2]**	**D22[+7]**		**D181[±14]**	**D366[±14]**		
Medical History@	X	X	X	X		X	X (if indicated)
Concomitant Medications	Xς	Xς	Xς	Xς		X (if within 21 days after last study vaccination and receipt of any non-study influenza vaccine will be recorded if within 180 days after the 2nd study vaccination)	X (if within 21 days after last study vaccination and receipt of any non-study influenza vaccine will be recorded if within 180 days after the 2nd study vaccination)
Vital Signs$ (Oral Temperature%, Pulse, and BP)						X (may be obtained if indicated)	X (may be obtained if indicated)
Physical Examination[3]	{X}	{X}	{X}	{X}		{X}	{X}
Venous Blood Collection for Clinical Safety Laboratory Evaluations~	X					X (if within 7 days after the last study vaccination)	X (if indicated)
Venous Blood Collection for Immunogenicity Assays		X	X	X		X(if within 21 days after last study vaccination	X(if within 21 days after last study vaccination
Serum Sample Collected for Future Research[4]	X	X	X	X		X(if within 21 days after last study vaccination	X(if within 21 days after last study vaccination
Safety Follow-up Phone Call					X		
Examine Vaccination Site	X					X (if within 7 days after last study vaccination)	X (if within 7 days after last study vaccination)
Post-Administration Reactogenicity Assessments						X (if within 7 days after last study vaccination)	X (if within 7 days after last study vaccination)
Review Memory Aid	X					X (if within 7 days after last study vaccination)	X (if within 7 days after last study vaccination)
AE/SAE Assessment	X&	X	X	X	X	X&	X&

@ Complete medical history will be obtained by interview of subjects at screening (optional) or on Day 1 prior to the first study vaccination and interim medical history will be obtained by interview of subjects at follow-up visits after the first study vaccination.

ς Receipt of non-study influenza vaccines will be solicited through approximately 180 days after the last study vaccination, and reported in the eCRF.

$ 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.

{} Targeted physical examination if indicated based on review of interim medical history.

~ Includes WBC, Hgb, PLT, ALT, T. Bili, Cr.

[Ψ] Subjects who do not receive the second or third 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 immunogenicity assays at approximately 21 and 180 days after their first study vaccination.

[4] For subjects who have consented to collected of serum for future use

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

Study Schedule, Group 3: Vaccination and Follow-up Periods

Study Visit Number	**V00**	**V01**	**V02**	**V03**	**V04[Ψ]**	**V05**	**V06**	**V07[Ψ]**	**V08**
Study Day post dose	**Screening (Optional) D -28 to -1**	**Enrollment Dose 1 D1**	**D4[±1]**	**D8[+2]**	**D22[+7]**	**D43[+7]**	**D64[+7]**	**D181[±14]**	**D366[±14]**
Obtain Informed Consent	X	X¬							
Collect Demographic Information	X	X†*							
Review Eligibility Criteria	X	X†¬[1]							
Medical History@	X	X†¬*		X	X	X	X	X	
Concomitant Medications	X[ς]	X†¬ς	X[ς]	X[ς]	X[ς]	X[ς]	X[ς]	X[ς]	
Vital Signs$ (Oral Temperature[%], Pulse, and BP)	X	X†							
Height and Weight	X	X†*							
Physical Examination[3]	X	{X}†*		{X}	{X}	{X}	{X}	{X}	
Urine or Serum Pregnancy Test	X^	X†^							
Venous Blood Collection for ESR	X	X≠*							
Venous Blood Collection for Clinical Safety Laboratory Evaluations~		X		X					
Venous Blood Collection for Immunogenicity Assays		X†			X			X	
Serum Sample Collected for Future Research[4]		X†		X	X	X	X	X	
Safety Follow-up Phone Call			X						X
Enrollment in AdvantageEDC[SM] and Randomization		X†							
Pre-Administration Reactogenicity Assessments		X†							
Vaccination		X							

Study Visit Number	**V00**	**V01**	**V02**	**V03**	**V04ᵠ**	**V05**	**V06**	**V07ᵠ**	**V08**
Study Day post dose	**Screening (Optional) D -28 to -1**	**Enrollment Dose 1 D1**	**D4[±1]**	**D8[+2]**	**D22[+7]**	**D43[+7]**	**D64[+7]**	**D181[±14]**	**D366[±14]**
20-minute Evaluation After Vaccination		X							
Examine Vaccination Site		X		X					
Post-Administration Reactogenicity Assessments		X							
Distribute Memory Aid and Study-Related Materials		X							
Review Memory Aid			X	X					
AE/SAE Assessment		X[&]	X[&]	X[&]	X	X	X	X	X

∞ Prior to study procedures.
† Prior to study vaccination.
[1] Review results of clinical screening (ESR) or 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 screening (optional) or on Day 1 prior to study vaccination and interim medical history will be obtained by interview of subjects at follow-up visits after the study vaccination.
[ς] Receipt of non-study influenza vaccines will be solicited through approximately 180 days after the study vaccination, and reported in the eCRF.
* Not required if done at the optional screening visit.
√ All current medications and medications taken within 60 days prior to signing the ICF.
$ Vital signs assessed on Day 1 prior to the 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.
[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, and nervous system.
{} Targeted physical examination if indicated based on review of interim medical history.
^ May be performed on all women of childbearing potential at screening (optional) and will be performed within 24 hours prior to study vaccination and results must be negative.
≠ To be performed locally by the site. The ESR value must be confirmed as <30 mm/hr prior to randomization and study vaccination.
~ Includes WBC, Hgb, PLT, ALT, T. Bili, Cr.
[4] For subjects who have consented to collected of serum for future use.
& Inclusive of reactogenicity assessments performed on the day of vaccination through 7 days after study vaccination.

Early Termination and Unscheduled Visits, Group 3

Study Visit Number	**Early Termination (if needed)**	**Unscheduled (if needed)**
Study Day post dose		
Medical History@	X	X (if indicated)

Concomitant Medications	X (if within 21 days after last study vaccination and receipt of any non-study influenza vaccine will be recorded if within 180 days after the 2nd study vaccination)	X (if within 21 days after last study vaccination and receipt of any non-study influenza vaccine will be recorded if within 180 days after the 2nd study)
Vital Signs (Oral Temperature[%], Pulse, and BP)	X (may be obtained if indicated)	X (may be obtained if indicated)
Physical Examination[3]	{X}	{X}
Venous Blood Collection for Clinical Safety Laboratory Evaluations~	X (if within 7 days after the last study vaccination)	X (if indicated)
Venous Blood Collection for Immunogenicity Assays	X (if within 21 days after last study vaccination)	X (if within 21 days after last study vaccination)
Serum Sample Collected for Future Research[4]	X(if within 21 days after last study vaccination	X(if within 21 days after last study vaccination
Examine Vaccination Site	X (if within 7 days after last study vaccination)	X (if within 7 days after last study vaccination)
Post-Administration Reactogenicity Assessments	X (if within 7 days after last study vaccination)	X (if within 7 days after last study vaccination)
Review Memory Aid	X (if within 7 days after last study vaccination)	X (if within 7 days after last study vaccination)
AE/SAE Assessment	X[&]	X[&]

[@] Complete medical history will be obtained by interview of subjects at screening (optional) or on Day 1 prior to study vaccination and interim medical history will be obtained by interview of subjects at follow-up visits after the study vaccination.
[$] Vital signs assessed on Day 1 prior to the 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.
{} Targeted physical examination if indicated based on review of interim medical history.
~ Includes WBC, Hgb, PLT, ALT, T. Bili, Cr.
[4] For subjects who have consented to collected of serum for future use.
[&] Inclusive of reactogenicity assessments performed on the day of vaccination through 7 days after study vaccination.

APPENDIX B: LIST OF POTENTIALLY IMMUNE-MEDIATED MEDICAL CONDITIONS

(also known as Adverse Events of Special Interest (AESIs))

Gastrointestinal disorders

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

Liver disorders

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

Metabolic diseases

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

Musculoskeletal disorders

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

- Systemic sclerosis

Neuroinflammatory disorders

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

Skin disorders

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

Vasculitides

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

Others

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