A Phase II Study to Assess the Safety, Reactogenicity and Immunogenicity of Different Prime-Boost Vaccination Schedules of 2013 and 2017 A/H7N9 Inactivated Influenza Vaccines Administered Intramuscularly with or without AS03 Adjuvant in Healthy Adults 19-50 Years of Age

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

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STATEMENT OF COMPLIANCE

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

- United States (US) 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 Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use E6(R2) Good Clinical Practice (ICH E6 GCP): Integrated Addendum to ICH E6(R1) Guidance for Industry, published in the Federal Register (83 Federal Register 8882 (2018)), including the latest finalized revision
- Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- National Institutes of Health (NIH) Office of Extramural Research, Research Involving Human Subjects, as applicable
- National Institute of Allergy and Infectious Diseases (NIAID) Clinical Terms of Award, as applicable
- Applicable Federal, State and Local Regulations and Guidance

SIGNATURE PAGE

The signature below provides the necessary 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 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 Institutional Review Board (IRB)/Institutional Ethics Committee (IEC) approval, except when necessary to protect the safety, rights or welfare of subjects.

Site Principal Investigator:

Signed: _____ Date: _____

Name
Title

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LIST OF ABBREVIATIONS

A/H1N1	Influenza A Virus of the H1N1 Subtype
A/H1N2v	Influenza A Virus of the H1N2 Variant 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/H5N6	Influenza A Virus of the H5N6 Subtype
A/H5N8	Influenza A Virus of the H5N8 Subtype
A/H7N1	Influenza A Virus of the H7N1 Subtype
A/H7N7	Influenza A Virus of the H7N7 Subtype
A/H7N9	Influenza A Virus of the H7N9 Subtype
A/H9N2	Influenza A Virus of the H9N2 Subtype
AE	Adverse Event/Adverse Experience
AESIs	Adverse Events of Special Interest
ALT	Alanine Aminotransferase
ANCA	Anti-Neutrophil Cytoplasmic Antibody
AS03	Adjuvant System (03)
BARDA	Biomedical Advanced Research and Development Authority
BLA	Biologics License Application
BMI	Body Mass Index
BP	Blood Pressure
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
COI	Conflict of Interest
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
EDC[SM]	Electronic Data Capture System
ELISA	Enzyme-Linked Immunosorbent Assay
ELISpot	Enzyme-Linked Immunosorbent Spot
ELLA	Enzyme-Linked Lectin Assay
ESR	Erythrocyte Sedimentation Rate
FACS	Fluorescence-Activated Cell Sorting
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
ICD-10	10th revision of the International Statistical Classification of Diseases and Related Health Problems
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICS	Intracellular Staining
IEC	Institutional Ethics Committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IIV	Inactivated Influenza Virus Vaccine
IIV3	Trivalent IIV
IM	Intramuscular(ly)
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor

IU/L	International Unit(s) per Liter
LLC	Limited Liability Company
MAAE	Medically-Attended Adverse Event
mcg	Microgram(s)
µL	Microliter(s)
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
NAI	Neuraminidase Inhibiting or Inhibition
Neut	Neutralizing or Neutralization
NIAID	National Institute of Allergy and Infectious Diseases, NIH
NIH	National Institutes of Health, DHHS
NK	Natural Killer
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
NOCMCs	New-Onset Chronic Medical Conditions
OER	Office of Extramural Research
OHRP	Office for Human Research Protections
OTC	Over the Counter
PBMC	Peripheral Blood Mononuclear Cell
PBS	Phosphate Buffered Saline
pH1N1	2009 H1N1 Influenza
PHI	Personal Health Information
PI	Principal Investigator
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
SMA	Secondary Medical Assessor
SOC	System Organ Class
SOP	Standard Operating Procedure
SP	Sanofi Pasteur
SRID	Single Radial Immunodiffusion
TBD	To Be Determined
T. Bili	Total Bilirubin
US	United States
V	Visit(s)
VTEU	Vaccine and Treatment Evaluation Unit
WBC	White Blood Cells
WHO	World Health Organization

PROTOCOL SUMMARY

Title:	A Phase II Study to Assess the Safety, Reactogenicity and Immunogenicity of Different Prime-Boost Vaccination Schedules of 2013 and 2017 A/H7N9 Inactivated Influenza Vaccines Administered Intramuscularly with or without AS03 Adjuvant in Healthy Adults 19-50 Years of Age
Phase:	II
Population:	Up to 180 males and non-pregnant females, 19 to 50 years of age, inclusive, who are in good health and meet all eligibility criteria
Number of Sites:	5 Vaccine and Treatment Evaluation Unit (VTEU) sites (and their subcontractors)
Study Duration:	Approximately 22 months
Subject Participation Duration:	Up to 18 months
Estimated Time to Complete Enrollment:	Approximately 12 weeks
Description of Agent:	• Monovalent inactivated split influenza 2013 (A/H7N9/Shanghai/2/2013) and 2017 (A/H7N9/Hong Kong/125/2017) A/H7N9 virus vaccines (2013 and 2017 A/H7N9 inactivated influenza virus vaccines [IIVs]) manufactured by Sanofi Pasteur (SP). • AS03 adjuvant manufactured by GlaxoSmithKline Biologicals (GSK). • Phosphate buffered saline (PBS) diluent manufactured by Patheon Manufacturing Services LLC.
Study Objectives:	**Primary:** <u>Safety:</u>

- To assess the safety and reactogenicity of 2013 and 2017 A/H7N9 IIVs given with or without AS03 adjuvant following receipt of each study vaccine.

Immunogenicity:

- To assess the serum hemagglutination inhibition (HAI) and neutralizing (Neut) antibody responses following receipt of the second study vaccine.

Secondary:

Safety:

- To assess unsolicited non-serious adverse events (AEs) following receipt of each study vaccine.
- To assess medically-attended adverse events (MAAEs), including new-onset chronic medical conditions (NOCMCs) and potentially immune-mediated medical conditions (PIMMCs), following receipt of each study vaccine.

Immunogenicity:

- To assess the kinetics and durability of serum HAI and Neut antibody responses following receipt of each study vaccine.

Exploratory:

Immunogenicity:

- To assess the effects of age, sex, body mass index (BMI), and prior receipt of seasonal or non-study pandemic influenza vaccine(s) on serum HAI and Neut antibody responses following receipt of the second study vaccine.
- To assess the neuraminidase (NA) content of the 2013 and 2017 A/H7N9 IIVs and determine, in at least a subset of samples, the serum antibody responses to N9 NA.
- To assess, in at least a subset of samples, HA stem-specific antibody responses.

- To assess, in at least a subset of samples, the cross-reactivity of serum HAI and Neut antibody responses to antigenically drifted variants of influenza A/H7 viruses.
- To assess, in at least a subset of samples, the frequency of influenza-specific (A/H7N9 antigens) IgA, IgG and IgM memory B cells (MBCs).
- To assess, in at least a subset of samples, the frequency of influenza-specific (A/H7N9 antigens) IgA, IgG and IgM plasmablasts (antibody-secreting cells [ASCs]).
- To assess, in at least a subset of samples, the multifunctional cytokine/chemokine profile of influenza A/H7N9-specific CD4 and CD8 T cells.
- To assess, in at least a subset of samples, the characterization of circulating T follicular helper (cT_{FH}) cells.
- To assess, in at least a subset of samples, the study vaccine-induced changes in populations and/or activation status of innate immune cells (monocytes, dendritic cells [DCs] and natural killer [NK] cells).
- To assess, in at least a subset of samples, the study vaccine-induced activation status of B cells.
- To assess, in at least a subset of samples, the B cell receptor repertoire and degree of somatic hypermutation generated in response to study vaccination.

Study Outcome Measures: **Primary:**

Safety:

- Occurrence of all serious adverse events (SAEs) from the time of the first study vaccination through approximately 12 months after the last study vaccination.
- Occurrence of solicited injection site and systemic reactogenicity events from the time of each study vaccination through 7 days after each study vaccination.

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

Immunogenicity:

- For HAI and Neut antibodies, percentage of subjects achieving seroconversion against the influenza A/H7N9 study vaccine viruses (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) approximately 21 days after the second study vaccination.
- For HAI and Neut antibodies, percentage of subjects achieving titer ≥1:40 against the influenza A/H7N9 study vaccine viruses approximately 21 days after the second study vaccination.
- Geometric mean titers (GMTs) of serum HAI and Neut antibodies against the influenza A/H7N9 study vaccine viruses approximately 21 days after the second study vaccination.

Secondary:

Safety:

- Occurrence of all unsolicited non-serious AEs from the time of each study vaccination through approximately 21 days after each study vaccination.
- Occurrence of all MAAEs, including NOCMCs and PIMMCs, from the time of the first study vaccination through approximately 12 months after the last study vaccination.

Immunogenicity:

- For HAI and Neut antibodies, percentage of subjects achieving seroconversion against the influenza A/H7N9 study vaccine viruses approximately 21 days after the first study vaccination as well as immediately prior to and approximately 180 days after the second study vaccination.

- For HAI and Neut antibodies, percentage of subjects achieving titer ≥1:40 against the influenza A/H7N9 study vaccine viruses immediately prior to each study vaccination, approximately 21 days after the first study vaccination and approximately 180 days after the second study vaccination.
- GMTs of serum HAI and Neut antibodies against the influenza A/H7N9 study vaccine viruses immediately prior to each study vaccination, approximately 21 days after the first study vaccination and approximately 180 days after the second study vaccination.

Exploratory:

Immunogenicity:

- For HAI and Neut antibodies, GMTs and percentage of subjects achieving seroconversion against the influenza A/H7N9 study vaccine viruses approximately 21 days after the second study vaccination, by age, sex, BMI, and prior receipt of seasonal or non-study pandemic influenza vaccine(s).
- GMTs and percentage of subjects achieving seroconversion (defined as four-fold change from baseline) of serum anti-NA (by enzyme-linked immunosorbent assay [ELISA]) or anti-neuraminidase inhibition (NAI) (by enzyme-linked lectin assay [ELLA]) antibodies immediately prior to and approximately 21 days after each study vaccination as well as approximately 180 days after the second study vaccination.
- Correlate the HA and/or NA content of 2013 and 2017 A/H7N9 IIVs with the elicited HA or N9 NA-specific antibody titer approximately 21 days after each study vaccination as well as immediately prior to and approximately 180 days after the second study vaccination.
- GMTs of HA stem-specific antibody immediately prior to and approximately 21 days after each study vaccination as well as approximately 180 days after the second study vaccination.

- For HAI and Neut antibodies, GMTs and percentage of subjects achieving seroconversion against antigenically drifted variants of influenza A/H7 viruses approximately 21 days after the second study vaccination.
- Percentage of influenza-specific (A/H7N9 antigens) IgA, IgG and IgM MBCs at baseline and approximately 90 and 180 days after the second study vaccination.
- Frequency of influenza-specific (A/H7N9 antigens) IgA, IgG and IgM plasmablasts (ASCs) present in circulation approximately 7 days after each study vaccination.
- Percentage of influenza A/H7N9-specific CD4 and CD8 T cells producing cytokines/chemokines immediately prior to and approximately 7 days after each study vaccination as well as approximately 90 days after the second study vaccination.
- Percentage of cT_{FH} cells producing cytokines/chemokines immediately prior to and approximately 3, 7 and 14 days after each study vaccination.
- Percentage and activation status of innate immune cells (monocytes, DCs and NK cells) immediately prior to and approximately 1, 3, 7 and 14 days after each study vaccination.
- Percentage of activated B cells immediately prior to and approximately 1, 3, 7 and 14 days after each study vaccination.
- Evaluation of B cell receptor repertoire and degree of somatic hypermutation of anti-HA (H7) and anti-NA (N9) antibodies at baseline and approximately 180 days after the second study vaccination.
- Correlation of the above exploratory immunologic parameters with HAI and Neut antibodies.

Description of Study Design: This is a Phase II clinical trial in up to 180 males and non-pregnant females, 19 to 50 years of age, inclusive, who are in good health and meet all eligibility criteria. This clinical trial is designed to assess the safety, reactogenicity and immunogenicity

of one or two doses of monovalent inactivated split influenza 2013 and 2017 A/H7N9 virus vaccines (2013 and 2017 A/H7N9 IIVs) manufactured by Sanofi Pasteur (SP), administered intramuscularly at different dosages (3.75 or 15 mcg of hemagglutinin (HA) per dose), given with or without AS03 adjuvant manufactured by GlaxoSmithKline Biologicals (GSK), using different heterologous and homologous prime-boost vaccination schedules. Phosphate buffered saline (PBS) diluent manufactured by Patheon Manufacturing Services LLC may be used to achieve targeted dosages.

Subjects who are influenza A/H7 vaccine/infection naïve by medical history will be randomly assigned to 1 of 6 treatment arms to receive one or two doses of the 2013 and 2017 A/H7N9 IIVs in different heterologous and homologous prime-boost combinations evaluating the interval between the priming (first) and boosting (second) doses (21 days vs. 4 months) and the presence of the adjuvant in the priming (first) and boosting (second) doses (see Table 1).

Reactogenicity will be measured by the occurrence of solicited injection site and systemic reactions from the time of each study vaccination through 7 days after each study vaccination. Unsolicited non-serious adverse events (AEs) will be collected from the time of each study vaccination through approximately 21 days after each study vaccination. Serious adverse events (SAEs) and medically-attended adverse events (MAAEs), including new-onset chronic medical conditions (NOCMCs) and potentially immune-mediated medical conditions (PIMMCs), will be collected from the time of the first study vaccination through approximately 12 months after the last study vaccination. Clinical safety laboratory evaluations (hematology and chemistry) will be performed on venous blood collected immediately prior to each study vaccination and approximately 7 days after each study vaccination.

Immunogenicity testing will include performing serological assays to assess hemagglutination inhibition (HAI), neutralizing (Neut), neuraminidase inhibition (NAI), neuraminidase (NA)-specific, and HA stem-specific antibody titers at multiple time points following each study vaccination. In addition, peripheral blood mononuclear

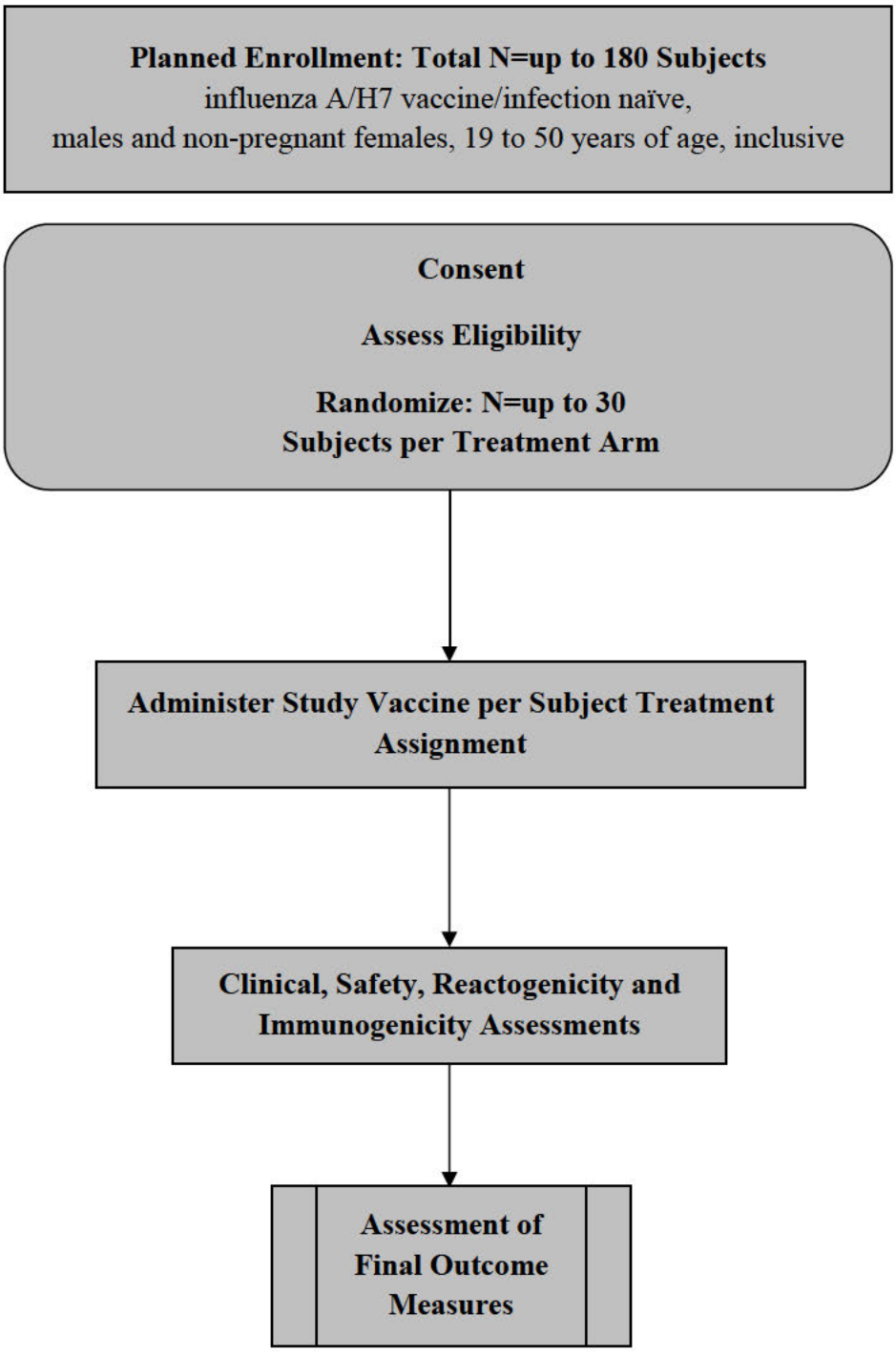
cells (PBMCs) will be used to determine broad immunologic responses and to correlate these responses with serological antibody responses described above in each of the treatment arms. These responses will include longitudinal assessments of the kinetics, magnitude, specificity, and/or quality of influenza-specific B and T cells, circulating T follicular helper (cT_{FH}) cells and innate immune cells (monocytes, dendritic cells [DCs] and natural killer [NK] cells) as well as the frequency of influenza-specific IgA, IgG and IgM plasmablasts (antibody-secreting cells [ASCs]) and B cell receptor somatic hypermutation and repertoire assessments. Venous blood will also be collected at multiple time points following each study vaccination for the future research use of serum, plasma and PBMCs.

In addition, we plan to determine the N9 NA-specific antibody response to study vaccination as well as assess the NA content of the 2013 and 2017 A/H7N9 IIVs using assays that are currently under development to determine if the NA content in a dose-specific manner correlates with the N9 NA-specific antibody response.

Table 1: Study Design

Influenza A/H7 Vaccine/Infection Naïve Subjects (Total N=180)		Treatment Arm/N	1st Study Vaccination Day 1	2nd Study Vaccination ~ Day 22 post Dose 1	2nd Study Vaccination ~ Day 121 post Dose 1
Study Vaccination Schedule	Heterologous Prime-Boost	1/30	2013 A/H7N9 IIV 3.75 mcg + AS03	2017 A/H7N9 IIV 3.75 mcg + AS03	
		2/30	2013 A/H7N9 IIV 3.75 mcg + AS03		2017 A/H7N9 IIV 3.75 mcg + AS03
		3/30	2013 A/H7N9 IIV 3.75 mcg + AS03		2017 A/H7N9 IIV 15 mcg
	Homologous Prime-Boost	4/30	2017 A/H7N9 IIV 3.75 mcg + AS03	2017 A/H7N9 IIV 3.75 mcg + AS03	
		5/30	2017 A/H7N9 IIV 3.75 mcg + AS03		2017 A/H7N9 IIV 3.75 mcg + AS03
		6/30	2017 A/H7N9 IIV 3.75 mcg + AS03		2017 A/H7N9 IIV 15 mcg

Figure 1: Schematic of Study Design



1 KEY ROLES

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Safety and Pharmacovigilance:	DMID Pharmacovigilance Group Clinical Research Operations and Management Support (CROMS)
Statistical and Data Coordinating Center:	The Emmes Company, LLC
Clinical Materials Services:	Fisher BioServices
Central (Clinical) Laboratory:	PPD Global Central Laboratories
HAI and Neut Antibody Assays Laboratory:	Southern Research
Cellular Immunology and Additional Serological Assays Laboratories:	To Be Determined (TBD)

2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

The continued emergence of novel influenza A viruses in humans including subtypes H5N1, H5N6, H3N2v, H1N2v, H7N7, H9N2, 2009 H1N1, and most recently H7N9, underscores the need for focused efforts to prepare for the next influenza pandemic [1-9]. 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 [10]. Excess mortality, high morbidity and social disruption were all noted during the 1957 influenza A/H2N2 and the 1968 influenza A/H3N2 pandemics [11]. 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 inactivated influenza virus vaccine (IIV) development programs that provided important insights into variables influencing the immune responses to immunization [12, 13]. Vaccine-associated factors potentially affecting the immunogenicity of IIVs that were noted during the 1976 experience and have been refined in subsequent years include the amount of viral hemagglutinin (HA) protein in the vaccine, the number and intervals of doses administered, the addition of immune stimulating components (i.e., adjuvants), and the manufacturing methods used to produce the vaccine (i.e., whole virus, split virus or purified surface antigen). Host-specific factors, including the recipient's age, their prior influenza infections and/or vaccinations, and the presence of underlying diseases and their treatments, all can influence the immune responses elicited by an influenza vaccine.

Serum antibodies targeting the influenza virus HA and neuraminidase (NA), the major surface glycoproteins on influenza viruses, play a key role in protective immunity to influenza virus infection [14]. Since protection against infection with seasonal influenza virus strains has been shown to correlate with both serum hemagglutination inhibition (HAI) and neutralizing (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 (NAI) antibodies in protection against disease [15]. In a recent human influenza

challenge study, serum NAI antibody levels were also identified as an independent correlate of protection against influenza illness [16]. In the current study, we plan to assess the NA content of the monovalent inactivated split influenza 2013 and 2017 A/H7N9 virus vaccines (2013 and 2017 A/H7N9 IIVs) and determine the correlation of the NA content at different vaccine dosages with the elicited humoral antibody responses to the N9 NA.

Several approaches have been used to increase the immunogenicity of IIVs. Standard-dose seasonal IIVs contain 7.5 to 15 mcg of HA antigen per seasonal influenza vaccine strain for children and adults up to 64 years of age. 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 [17-25]. Higher HA dosage influenza vaccines can lead to enhanced antibody responses in the elderly [26]. In 2009, a high-dose seasonal IIV containing 4 times the standard HA antigen per seasonal influenza vaccine strain was approved in the United States (US) for use in individuals 65 years of age and older.

In general, clinical studies evaluating vaccines made from novel avian influenza viruses (e.g., A/H5N1, A/H7N7, 2013 A/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 [27, 28]. Due to the poor immunogenicity of A/H5 and A/H7 vaccines, the inclusion of adjuvants was evaluated to assess their ability to boost anti-viral serum 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 [29-31]. In contrast, the use of oil-in-water emulsion adjuvants, most notably proprietary adjuvants AS03 and MF59 produced by GlaxoSmithKline Biologicals (GSK) and Novartis (now Seqirus), respectively, has resulted in increased antibody responses to IIVs containing novel HAs in numerous clinical trials [32-36]. 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 geometric mean titers (GMTs) in subjects who received the adjuvanted formulations [34]. 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 treatment arms only the 30 mcg formulation met the CHMP criterion for seroconversion [34]. GSK received approval for the registration of a pre-pandemic AS03-adjuvanted, monovalent inactivated influenza A/H5N1 virus vaccine by European regulatory authorities in 2008 and FDA approval of their Biologics License Applications (BLA) for an 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 influenza 2009 A/H1N1 virus vaccine (Pandemrix™) and Novartis' egg-derived MF59-adjuvanted, monovalent inactivated influenza 2009 A/H1N1 virus vaccine (FOCETRIA™). These adjuvanted monovalent inactivated influenza 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 [29]. 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 [37-45]. See Section 2.3.1 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 [46-51]. In response to emerging influenza A/H5N8 viruses that have caused extensive outbreaks in domestic poultry and wild birds in South East Asia [52, 53], NIAID is also conducting two ongoing clinical trials with an A/H5N8 vaccine produced by bioCSL (now Seqirus) administered with either AS03 (GSK) or MF59 (Seqirus) adjuvants in healthy subjects, 19 to 64 years of age (DMID Protocol 15-0064; NCT02624219 and DMID Protocol 15-0066; NCT03014310).

Since March of 2013 [54], 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. China is currently experiencing it's "sixth wave" of A/H7N9 infections, and as of March 2, 2018, a total of 1,567 laboratory-confirmed human infections with avian influenza A/H7N9 viruses have been reported by the World Health Organization [55]. 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 [56]. 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 [56]. Laboratory studies have shown that influenza A/H7N9 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 [57, 58].

During the "fifth wave" of outbreaks which began in October 2016, more human cases of A/H7N9 infection were reported in China than during any prior A/H7N9 epidemic wave [55]. In addition, an antigenically distinct lineage of these fifth wave influenza A/H7N9 viruses known as the Yangtze River Delta lineage has recently emerged and has been associated with an increasing number of human cases [59].

The US Department of Health and Human Services (DHHS) recently determined influenza A/H7N9 virus as having a significant potential to cause a pandemic, and the greatest risk of causing severe disease. As a result, DHHS has supported the production of fifth wave pre-pandemic A/H7N9 IIVs for the US stockpile and for an assessment of safety and immunogenicity in clinical trials.

2.1.1 Public Readiness and Emergency Preparedness Act

For this protocol, the study products (2013 and 2017 A/H7N9 IIVs manufactured by Sanofi Pasteur and AS03 adjuvant 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 2013 and 2017 A/H7N9 IIVs with or without AS03 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 2013 and 2017 A/H7N9 IIVs with or without AS03 adjuvant may request benefits from the CICP. A serious physical injury means an injury that is life-threatening, or 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, and the Department of Veterans Affairs or Workers' Compensation programs do not 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 US 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 or are currently being evaluated by NIAID's VTEU sites to assess their safety, reactogenicity and immunogenicity when mixed prior to administration with either AS03 or MF59 oil-in-water adjuvants manufactured by GSK and Seqirus, respectively. In general, these "mix and match" clinical trials have demonstrated that adjuvant use results in a significant dose-sparing effect.

The large number of human infections starting with the "fifth wave" of outbreaks in late 2016 has increased the pandemic risk potential of influenza A/H7N9 viruses circulating in China. The Yangtze River Delta lineage, a distinct A/H7N9 viral lineage, has now emerged and has been associated with many of the fifth wave cases. Fifth wave A/H7N9 viruses have led to a broader geographic spread of infected birds and human cases within China than previously reported. Further, several influenza A/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 [56, 59]. To date, no cases of A/H7N9 from the new viral 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 influenza A/H7N9 viruses and serological studies indicate that the stockpiled 2013 A/H7N9 IIV manufactured several years ago does not induce protective HAI or Neut antibodies against the Yangtze River Delta lineage. Hence, there is broad consensus across DHHS and interagency leadership that a new vaccine should be developed that would be effective against the currently predominating influenza A/H7N9 viruses.

Several candidate vaccine viruses are under evaluation by the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) H5 Reference Laboratories Network. Under contract to BARDA/DHHS, Sanofi Pasteur has produced monovalent inactivated split influenza 2013 and 2017 A/H7N9 virus vaccines (2013 and 2017 A/H7N9 IIVs) using largely the same manufacturing process as its licensed, seasonal trivalent IIV (IIV3). The availability of the US Government-stockpiled AS03 (GSK) oil-in-water adjuvant provides an opportunity to determine if dose-sparing effects occur when mixing the Sanofi Pasteur 2013 and 2017 A/H7N9 IIVs with the GSK AS03 adjuvant. See Sections 2.3.1 and 6.1 for additional details on the 2013 and 2017 A/H7N9 IIVs.

Heterologous prime-boost vaccination regimens have shown considerable promise in expanding the breadth and durability of cross-clade antibody responses [60, 61]. In addition, the use of adjuvants and extending the interval between the priming (first) and boosting (second) doses of vaccine have also led to more robust cross-clade antibody responses [60-63].

The goal of this clinical trial is to assess in healthy adults, 19 to 50 years of age, the safety, reactogenicity and immunogenicity of one or two doses 2013 and 2017 A/H7N9 IIVs, administered intramuscularly at different dosages (3.75 or 15 mcg of hemagglutinin (HA) per dose), given with or without AS03 adjuvant, using different heterologous and homologous prime-boost vaccination schedules to evaluate the study vaccine dosage, dose-sparing potential of the adjuvant, optimal prime-boost interval for immunogenicity (two doses administered 21 days vs. 4 months apart), and priming effects of different A/H7N9 IIVs. In addition to assessing antigen-sparing strategies, another goal of this study is to assess in at least a subset of samples, if serum immunoglobulin elicited by the 2013 and 2017 A/H7N9 IIVs recognize antigenically drifted variants of influenza A/H7 viruses. Since antibodies targeting the NA may represent an independent correlate of protection against influenza infection [15, 16], we plan to assess the NA content of the 2013 and 2017 A/H7N9 IIVs and determine if there is a dose-specific correlation of the NA content with the elicited humoral antibody responses to the N9 NA.

This clinical trial will also investigate novel methods for identifying and assessing alternative cellular correlates of protection against influenza infection. These will include longitudinal assessments of: 1) the kinetics, magnitude, specificity, and/or quality of influenza-specific B and T cells, cT_{FH} cells and innate immune cells (monocytes, DCs and NK cells); 2) the frequency of

influenza-specific IgA, IgG and IgM plasmablasts (ASCs); and 3) B cell receptor somatic hypermutation and repertoire assessments.

Based on previously conducted studies with a 2013 A/H7N9 IIV manufactured by Sanofi Pasteur administered with or without AS03, we anticipate that two doses of the 2013 and 2017 A/H7N9 IIVs administered IM at different dosages with or without AS03 adjuvant using different prime-boost vaccination schedules will be well-tolerated and more immunogenic compared to the non-adjuvanted study vaccine in healthy adults.

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 intramuscular (IM) injection, possible reactions to the 2013 and 2017 H7N9 IIVs, with or without 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 erythrocyte sedimentation rate (ESR). Clinical 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 each study vaccination, but results will not be reviewed until after each 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 treatment arms [64] than in the non-adjuvanted treatment arms and there is potentially a higher risk for AEs to occur more frequently in the higher dose influenza antigen treatment arms than in the lower dose influenza antigen treatment arms.

The 2017 A/H7N9 IIV to be used in this clinical trial has not been tested for safety in animals; however, it is currently being evaluated in humans. The Division of Microbiology and Infectious Diseases (DMID), NIAID is sponsoring two Phase II clinical trials in healthy subjects to assess the safety, reactogenicity and immunogenicity of IM doses of the 2017 A/H7N9 IIV produced by Sanofi Pasteur, Swiftwater, PA, administered with or without the AS03 adjuvant produced by GSK and co-administered sequentially or simultaneously with licensed, seasonal influenza vaccine (Fluzone® Quadrivalent Influenza Vaccine) produced by Sanofi Pasteur, Swiftwater, PA (DMID Protocols: 17-0075; NCT03312231, 17-0077; NCT03318315).

The 2013 A/H7N9 IIV to be used in this clinical trial is currently being tested for safety in animals. In addition, DMID, NIAID has sponsored at least five Phase II clinical trials to assess the safety, reactogenicity and immunogenicity of IM doses of the 2013 A/H7N9 IIV produced by Sanofi Pasteur, Swiftwater, PA, administered with or without either AS03 (GSK) or MF59 (Seqirus) adjuvants in healthy subjects (DMID Protocols: 13-0032; NCT01938742, 13-0033; NCT01942265, 13-0034; NCT02213354, 13-0044; NCT02586792, and 14-0015; NCT02921997). Overall, the study products administered in these clinical trials were generally safe and well-tolerated.

For DMID Protocol 13-0032, nine SAEs were reported. All were assessed as being not related to study product. Two cases of Autoimmune thyroiditis (Hashimoto's disease/Hashimoto's thyroiditis), classified as 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) whereas the other 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 study vaccination, but both disorders received the diagnosis after study vaccination.

For DMID Protocol 13-0034, seventy-five SAEs were reported. All were assessed as being not related to study product. Two AESIs were reported in this clinical trial: guttate psoriasis vulgaris and lichen planus; both were assessed as related to study product.

For DMID Protocol 13-0044, no SAEs were reported. No AESIs were reported, since this clinical trial tested the unadjuvanted 2013 A/H7N9 IIV.

For DMID Protocol 14-0015, one SAE was reported. It was assessed as not related to study product. No AESIs were reported in this clinical trial.

The monovalent split 2013 A/H7N9 IIV to be used in this clinical trial was derived from the influenza virus A/Shanghai/2/2013 (H7N9). The monovalent split 2017 A/H7N9 IIV to be used in this clinical trial was derived from the influenza virus A/Hong Kong/125/2017 (H7N9). The manufacturing process for the production of these investigational A/H7N9 vaccines is similar to the process used to produce the licensed, Influenza Virus Vaccine Fluzone® family of products, except for a minor modification in the PBS diluent in the formulation step of the 2013 A/H7N9 IIV that was made according to previous experiences of manufacturing of monovalent pandemic vaccines. As such, the safety profile of the candidate A/H7N9 vaccines should be similar to the current Fluzone® vaccine.

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 their monovalent split 2013 A/H7N9 IIV administered with or without AS03 or 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 (A/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 (A/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 [65]. Interestingly, although vaccination rates have increased in the last 10 years, the numbers of reported cases of vaccine-associated GBS have declined [66]. A recent study in Canada showed that the 2009 A/H1N1 vaccine was associated with a small but significant risk of GBS in persons 50 years of age and older [67]. An active, population-based surveillance study conducted in the US during the 2009-2010 influenza season found less than 1 excess GBS case per million doses of 2009 A/H1N1 vaccine administered – a rate similar to that associated with some previously administered annual influenza vaccines [68-70]. Another study using the Medicare system showed an elevated risk of GBS with monovalent 2009 A/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) [71]. An international collaboration study also supported a conclusion of an association between 2009 A/H1N1 vaccination and GBS [72]. It is unknown if the administration

of the 2013 and 2017 A/H7N9 IIVs 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 GSK AS03 Adjuvant Investigator's Brochure 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 adult (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 injection site 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 AS03-adjuvanted H5N1 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 A/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 [73]. 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**, Guillain-Barré syndrome*

      **Spontaneous reports of Guillain-Barré syndrome have been received following vaccination with Arepanrix™ (H1N1); however, a causal association between vaccination and Guillain-Barré syndrome has not been established. Data from a post-marketing epidemiological study in Canada indicate a small but significant increased relative risk of Guillain-Barré syndrome 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 inter-pandemic (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 Guillain-Barré syndrome

- 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 are no available data related to the risks of exposure to A/H7N9 IIVs 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 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 2013 and 2017 A/H7N9 IIVs with or without AS03 adjuvant. Vaccination using the 2013 and 2017 A/H7N9 IIVs with or without AS03 adjuvant may or may not provide protection against a serious disease with the influenza 2013 and 2017 A/H7N9 viruses, should the subject be exposed. The duration of any such protection is currently unknown. The 2013 and 2017 A/H7N9 IIVs with or without AS03

adjuvant are 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 2013 or 2017 A/H7N9 vaccination occurs.

3 STUDY OBJECTIVES AND OUTCOME MEASURES

3.1 Study Objectives

3.1.1 Primary

Safety:

- To assess the safety and reactogenicity of 2013 and 2017 A/H7N9 IIVs given with or without AS03 adjuvant following receipt of each study vaccine.

Immunogenicity:

- To assess the serum hemagglutination inhibition (HAI) and neutralizing (Neut) antibody responses following receipt of the second study vaccine.

3.1.2 Secondary

Safety:

- To assess unsolicited non-serious adverse events (AEs) following receipt of each study vaccine.
- To assess medically-attended adverse events (MAAEs), including new-onset chronic medical conditions (NOCMCs) and potentially immune-mediated medical conditions (PIMMCs), following receipt of each study vaccine.

Immunogenicity:

- To assess the kinetics and durability of serum HAI and Neut antibody responses following receipt of each study vaccine.

3.1.3 Exploratory

Immunogenicity:

- To assess the effects of age, sex, body mass index (BMI), and prior receipt of seasonal or non-study pandemic influenza vaccine(s) on serum HAI and Neut antibody responses following receipt of the second study vaccine.

- To assess the neuraminidase (NA) content of the 2013 and 2017 A/H7N9 IIVs and determine, in at least a subset of samples, the serum antibody responses to N9 NA.

- To assess, in at least a subset of samples, HA stem-specific antibody responses.

- To assess, in at least a subset of samples, the cross-reactivity of serum HAI and Neut antibody responses to antigenically drifted variants of influenza A/H7 viruses.

- To assess, in at least a subset of samples, the frequency of influenza-specific (A/H7N9 antigens) IgA, IgG and IgM memory B cells (MBCs).

- To assess, in at least a subset of samples, the frequency of influenza-specific (A/H7N9 antigens) IgA, IgG and IgM plasmablasts (antibody-secreting cells [ASCs]).

- To assess, in at least a subset of samples, the multifunctional cytokine/chemokine profile of influenza A/H7N9-specific CD4 and CD8 T cells.

- To assess, in at least a subset of samples, the characterization of circulating T follicular helper (cT_{FH}) cells.

- To assess, in at least a subset of samples, the study vaccine-induced changes in populations and/or activation status of innate immune cells (monocytes, dendritic cells [DCs] and natural killer [NK] cells).

- To assess, in at least a subset of samples, the study vaccine-induced activation status of B cells.

- To assess, in at least a subset of samples, the B cell receptor repertoire and degree of somatic hypermutation generated in response to study vaccination.

3.2 Study Outcome Measures

3.2.1 Primary

Safety:

- Occurrence of all serious adverse events (SAEs) from the time of the first study vaccination through approximately 12 months after the last study vaccination.

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

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

Immunogenicity:

- For HAI and Neut antibodies, percentage of subjects achieving seroconversion against the influenza A/H7N9 study vaccine viruses (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) approximately 21 days after the second study vaccination.

- For HAI and Neut antibodies, percentage of subjects achieving titer ≥1:40 against the influenza A/H7N9 study vaccine viruses approximately 21 days after the second study vaccination.

- Geometric mean titers (GMTs) of serum HAI and Neut antibodies against the influenza A/H7N9 study vaccine viruses approximately 21 days after the second study vaccination.

3.2.2 Secondary

Safety:

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

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

Immunogenicity:

- For HAI and Neut antibodies, percentage of subjects achieving seroconversion against the influenza A/H7N9 study vaccine viruses approximately 21 days after the first study vaccination as well as immediately prior to and approximately 180 days after the second study vaccination.

- For HAI and Neut antibodies, percentage of subjects achieving titer ≥1:40 against the influenza A/H7N9 study vaccine viruses immediately prior to each study vaccination, approximately 21 days after the first study vaccination and approximately 180 days after the second study vaccination.

- GMTs of serum HAI and Neut antibodies against the influenza A/H7N9 study vaccine viruses immediately prior to each study vaccination, approximately 21 days after the first study vaccination and approximately 180 days after the second study vaccination.

3.2.3 Exploratory

Immunogenicity:

- For HAI and Neut antibodies, GMTs and percentage of subjects achieving seroconversion against the influenza A/H7N9 study vaccine viruses approximately 21 days after the second study vaccination, by age, sex, BMI, and prior receipt of seasonal or non-study pandemic influenza vaccine(s).

- GMTs and percentage of subjects achieving seroconversion (defined as four-fold change from baseline) of serum anti-NA (by enzyme-linked immunosorbent assay [ELISA]) or anti-neuraminidase inhibition (NAI) (by enzyme-linked lectin assay [ELLA]) antibodies immediately prior to and approximately 21 days after each study vaccination as well as approximately 180 days after the second study vaccination.

- Correlate the HA and/or NA content of 2013 and 2017 A/H7N9 IIVs with the elicited HA or N9 NA-specific antibody titer approximately 21 days after each study vaccination as well as immediately prior to and approximately 180 days after the second study vaccination.

- GMTs of HA stem-specific antibody immediately prior to and approximately 21 days after each study vaccination as well as approximately 180 days after the second study vaccination.

- For HAI and Neut antibodies, GMTs and percentage of subjects achieving seroconversion against antigenically drifted variants of influenza A/H7 viruses approximately 21 days after the second study vaccination.

- Percentage of influenza-specific (A/H7N9 antigens) IgA, IgG and IgM MBCs at baseline and approximately 90 and 180 days after the second study vaccination.

- Frequency of influenza-specific (A/H7N9 antigens) IgA, IgG and IgM plasmablasts (ASCs) present in circulation approximately 7 days after each study vaccination.

- Percentage of influenza A/H7N9-specific CD4 and CD8 T cells producing cytokines/chemokines immediately prior to and approximately 7 days after each study vaccination as well as approximately 90 days after the second study vaccination.

- Percentage of cT_{FH} cells producing cytokines/chemokines immediately prior to and approximately 3, 7 and 14 days after each study vaccination.

- Percentage and activation status of innate immune cells (monocytes, DCs and NK cells) immediately prior to and approximately 1, 3, 7 and 14 days after each study vaccination.

- Percentage of activated B cells immediately prior to and approximately 1, 3, 7 and 14 days after each study vaccination.

- Evaluation of B cell receptor repertoire and degree of somatic hypermutation of anti-HA (H7) and anti-NA (N9) antibodies at baseline and approximately 180 days after the second study vaccination.

- Correlation of the above exploratory immunologic parameters with HAI and Neut antibodies.

4 STUDY DESIGN

This is a Phase II clinical trial in up to 180 males and non-pregnant females, 19 to 50 years of age, inclusive, who are in good health and meet all eligibility criteria. This clinical trial is designed to assess the safety, reactogenicity and immunogenicity of one or two doses of monovalent inactivated split influenza 2013 and 2017 A/H7N9 virus vaccines (2013 and 2017 A/H7N9 IIVs) manufactured by Sanofi Pasteur (SP), administered intramuscularly at different dosages (3.75 or 15 mcg of hemagglutinin (HA) per dose), given with or without AS03 adjuvant manufactured by GlaxoSmithKline Biologicals (GSK), using different heterologous and homologous prime-boost vaccination schedules. Phosphate buffered saline (PBS) diluent manufactured by Patheon Manufacturing Services LLC may be used to achieve targeted dosages.

Subjects who are influenza A/H7 vaccine/infection naïve by medical history will be randomly assigned to 1 of 6 treatment arms to receive one or two doses of the 2013 and 2017 A/H7N9 IIVs in different heterologous and homologous prime-boost combinations evaluating the interval between the priming (first) and boosting (second) doses (21 days vs. 4 months) and the presence of the adjuvant in the priming (first) and boosting (second) doses (see Table 1).

Reactogenicity will be measured by the occurrence of solicited injection site and systemic reactions from the time of each study vaccination through 7 days after each study vaccination. Unsolicited non-serious adverse events (AEs) will be collected from the time of each study vaccination through approximately 21 days after each study vaccination. Serious adverse events (SAEs) and medically-attended adverse events (MAAEs), including new-onset chronic medical conditions (NOCMCs) and potentially immune-mediated medical conditions (PIMMCs), will be collected from the time of the first study vaccination through approximately 12 months after the last study vaccination. Clinical safety laboratory evaluations (hematology and chemistry) will be performed on venous blood collected immediately prior to each study vaccination and approximately 7 days after each study vaccination.

Immunogenicity testing will include performing serological assays to assess hemagglutination inhibition (HAI), neutralizing (Neut), neuraminidase inhibition (NAI), neuraminidase (NA)-specific, and HA stem-specific antibody titers at multiple time points following each study vaccination. In addition, peripheral blood mononuclear cells (PBMCs) will be used to determine broad immunologic responses and to correlate these responses with serological antibody responses described above in each of the treatment arms. These responses will include longitudinal assessments of the kinetics, magnitude, specificity, and/or quality of influenza-specific B and T cells, circulating T follicular helper (cT_{FH}) cells and innate immune cells (monocytes, dendritic cells [DCs] and natural killer [NK] cells) as well as the frequency of influenza-specific IgA, IgG and IgM plasmablasts (antibody-secreting cells [ASCs]) and B cell receptor somatic hypermutation and repertoire assessments. Venous blood will also be collected

at multiple time points following each study vaccination for the future research use of serum, plasma and PBMCs.

In addition, we plan to determine the N9 NA-specific antibody response to study vaccination as well as assess the NA content of the 2013 and 2017 A/H7N9 IIVs using assays that are currently under development to determine if the NA content in a dose-specific manner correlates with the N9 NA-specific antibody response.

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

5 STUDY ENROLLMENT AND WITHDRAWAL

Up to 180 males and non-pregnant females, 19 to 50 years of age, inclusive, who are in good health and meet all eligibility criteria will be enrolled at up to 5 VTEU sites (and their subcontractors) 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 each of the participating VTEU sites. Other forms and/or mechanisms of recruitment may also be used. The IRB will approve all materials prior to use.

Subject Inclusion and Exclusion Criteria must be assessed by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site principal investigator (PI) or sub-investigator.

No exemptions are granted on Subject Inclusion or Exclusion Criteria in DMID-sponsored studies. Questions about eligibility should be directed toward the DMID Medical Officer.

5.1 Eligibility Criteria

5.1.1 Subject Inclusion Criteria

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

1. Provide written informed consent prior to initiation of any study procedures.
2. Are able to understand and comply with planned study procedures and be available for all study visits.
3. Must agree to the collection of venous blood per protocol.
4. Must agree to have residual specimens and samples/specimens collected during this trial specifically for the purpose of future research stored for future research use.
5. Are males or non-pregnant females, 19 to 50 years of age, inclusive.
6. 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 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 PI 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 PI 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 (except inhaled corticosteroids as outlined in the Subject Exclusion Criteria (see Section 5.1.2)) as well as herbals, vitamins and supplements are permitted.*

7. Oral temperature is less than 100.0°F.
8. Pulse is 47 to 100 beats per minute, inclusive.
9. Systolic blood pressure is 85 to 150 mmHg, inclusive.
10. Diastolic blood pressure is 55 to 95 mmHg, inclusive.
11. ESR is less than 30 mm per hour.
12. 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 has passed since 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/cervical cap ***with*** *spermicide, effective intrauterine devices, NuvaRing®, and licensed hormonal methods such as implants, injectables or oral contraceptives ("the pill").*

13. 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 PI or appropriate sub-investigator, within 72 hours prior to study vaccination.

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

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

[5]*Including acute or chronic medical disease or condition, defined as persisting for at least 90 days, that would place the subject at an unacceptable risk of injury, render the subject unable to meet the requirements of the protocol, or may interfere with the evaluation of responses or the subject's successful completion of this trial.*

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

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

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

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

7. Have known hypersensitivity or allergy to eggs, egg or chicken protein, 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 C: 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[7] with subject compliance or safety evaluations.

[7]*As determined by the site PI or appropriate sub-investigator.*

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[8] within 30 days prior to each study vaccination.

    [8]High-dose defined as per age as using inhaled high-dose per reference chart in the National Heart, Lung and Blood Institute Guidelines for the Diagnosis and Management of Asthma (EPR-3) or other lists published in UPTODATE.

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 licensed, seasonal IIVs) within 14 days before or after each study vaccination.

20. Received or plan to receive a licensed, seasonal IIV within 21 days before or after each study vaccination.

21. Received immunoglobulin or other blood products (except Rho D immunoglobulin) within 90 days prior to each study vaccination.

22. Received an experimental agent[9] within 30 days prior to the first study vaccination or expect to receive an experimental agent[10] during the trial-reporting period[11].

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

    [10]Other than from participation in this trial.

    [11]Approximately 12 months after the last study vaccination.

23. Are participating or plan to participate in another clinical trial with an interventional agent[12] that will be received during the trial-reporting period[13].

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

    [13]Approximately 12 months after the last study vaccination.

24. Received or plan to receive an influenza A/H7 vaccine[14] or have a history of influenza A/H7 subtype infection.

    [14]And assigned to a treatment arm receiving influenza A/H7 vaccine, i.e., does not apply to documented placebo recipients.

25. Had substantial direct contact[15] with live or freshly slaughtered poultry or pigeons while in mainland China within the past five years.

    [15]*Substantial direct contact is defined as visited a poultry farm and/or a live poultry market.*

26. Occupational exposure to or substantial direct physical contact[16] with birds in the past year and through 21 days after the last study vaccination.

    [16]*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 the time of each study vaccination through 21 days after each study vaccination.

5.2 Treatment Assignment Procedures

5.2.1 Enrollment and Randomization Procedures

Per ICH E6 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 1 of 6 treatment arms, stratified by the participating VTEU site and prior receipt of licensed, seasonal influenza vaccine (defined as receipt of at least one of the 2017-2018 and/or 2018-2019 licensed, seasonal influenza vaccines). Subjects will receive two study vaccinations per their randomized treatment assignment (see Table 1).

Enrollment of subjects will be done online using the enrollment module of AdvantageEDC^{SM}. The randomization code will be prepared by statisticians at the SDCC and included in the enrollment module for this trial. AdvantageEDC^{SM} will assign each subject to a treatment arm after the demographic and eligibility data have been entered into the system. A designated individual at each participating VTEU site will be provided with a code list for emergency unblinding purposes, which will be kept in a secure place.

Instructions for use of the enrollment module are included in the AdvantageEDC^{SM} User's Guide. Manual back-up procedures and instructions are provided for use in the event that a

participating VTEU site temporarily loses access to the Internet or the online enrollment system is unavailable.

5.2.2 Masking Procedures

This is a partially-blinded clinical trial.

Subjects, site investigators and study personnel performing any study-related assessments following study vaccine administration to the subject are partially-blinded (blinded to treatment assignment and unblinded to treatment interval). Laboratory personnel performing HAI and Neut antibody assays will receive serum specimens blinded to subject ID number and specimen visit number.

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

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

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

5.2.3 Reasons for Withdrawals and Discontinuation of Study Product Administration

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

The site PI or appropriate sub-investigator may also withdraw a subject from receiving the study vaccine for any reason.

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 PI 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.
- Subject withdrawal of consent.
- Subject lost to follow-up.
- Termination of this trial.
- As deemed necessary by the site PI or appropriate sub-investigator for noncompliance or other reasons.
- New information becomes available that makes further participation unsafe.

The second study vaccination 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 PI 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 second study vaccination should be postponed/deferred until signs, symptoms or acute illness have/has resolved, or are/is improving as further specified below, and if within the acceptable protocol-specified window for the Dose 2 visit. 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 the Dose 2 visit, and, in the opinion of the site PI or appropriate sub-investigator, the residual symptoms will not interfere with the ability to assess safety parameters as required by the protocol, the subject may receive the second study vaccination without further approval from the DMID Medical Officer. No exceptions to the protocol-specified window will be made.

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

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

- Any unresolved or ongoing Grade 2 solicited or unsolicited AE that does not decrease to Grade 1 or less prior to the second study vaccination. Note: An unresolved or ongoing Grade 1 solicited or unsolicited AE is permissible following the documented determination by the site PI or appropriate sub-investigator, that it would not render study vaccination unsafe or interfere with the evaluation of responses.

- Grade 3 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. Note: Any clinical safety laboratory parameter may be re-evaluated only once at the central (clinical) laboratory in order to assess eligibility prior to the second study vaccination. If the clinical safety laboratory value decreases to Grade 2 or less, the subject may receive the second study vaccination. The second study vaccination should be scheduled to occur within the acceptable protocol-specified window for the Dose 2 visit. 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 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.

- Subject refusal of further study vaccination.

- Subject withdrawal of consent.

- Subject lost to follow-up.

- Termination of this trial.

- As deemed necessary by the site PI or appropriate sub-investigator for noncompliance or other reasons.

- New information becomes available that makes further participation unsafe.

5.2.4 Handling of Withdrawals and Discontinuation of Study Product Administration

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 8.4.

Although subjects are free to withdraw at any time or may be withdrawn by the site PI or appropriate sub-investigator at any time (see Section 5.2.3), those subjects who receive only one dose of study vaccine will be encouraged to remain in this trial for follow-up safety assessments (may be conducted by phone call rather than in person) continuing through approximately 12 months after their last study vaccination. These subjects will also be encouraged to provide a venous blood sample for serological assays approximately 21 and 180 days after their last study vaccination. 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.

The site PI or appropriate sub-investigator will inform the subject that already collected data will be retained and analyzed even if the subject withdraws or is withdrawn from this study.

5.2.5 Subject Replacement

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.

5.2.6 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.

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

6 STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

6.1 Study Product Description

2013 A/H7N9 IIV

Sanofi Pasteur has developed a monovalent split 2013 A/H7N9 IIV manufactured using a reverse genetics-derived reassortant candidate vaccine virus, IDCDC RG32A (H7N9), containing the HA and NA from avian influenza A/Shanghai/2/2013 (H7N9) and the PB2, PB1, PA, NP, M and NS from A/Puerto Rico/8/1934 (H1N1). The manufacturing processes used for the investigational vaccine are similar to the Fluzone® family of licensed processes, except for a minor modification in the PBS diluent in the formulation step that was made according to previous experiences of manufacturing of monovalent pandemic vaccines.

2017 A/H7N9 IIV

Sanofi Pasteur has developed a monovalent split 2017 A/H7N9 IIV manufactured using a reverse genetics-derived reassortant candidate vaccine virus, IDCDC RG56B (H7N9), containing the HA and NA from low pathogenic avian 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 processes used for the investigational vaccine are similar to the Fluzone® family of licensed processes.

PBS Diluent

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

AS03 Adjuvant [Adjuvant System (03)]

[redacted]

6.1.1 Acquisition

2013 and 2017 A/H7N9 IIVs will be provided by Sanofi Pasteur under contract to BARDA/DHHS.

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

Upon request by DMID, 2013 and 2017 A/H7N9 IIVs 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

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

2013 and 2017 A/H7N9 IIVs, PBS diluent, AS03 adjuvant, and sterile empty vials for study vaccine preparation will be provided through the DMID CMS to the participating VTEU sites prior to the start of this trial upon request and with prior approval from DMID. Should the site PI require additional 2103 and 2017 A/H7N9 IIVs, PBS diluent, AS03 adjuvant, or sterile empty vials during this trial, further instructions are provided in the protocol-specific MOP.

6.1.2 Formulation, Storage, Packaging, and Labeling

2013 A/H7N9 IIV

Investigational influenza virus A/Shanghai vaccine (H7N9), a monovalent type A inactivated vaccine for intramuscular (IM) use, is a sterile suspension prepared from pandemic influenza virus candidate vaccine propagated in embryonated chicken eggs. Antibiotics are not used in the manufacture of this vaccine. This vaccine contains no preservative (thimerosal). There is no gelatin added to this vaccine in the manufacturing process. No components of this vaccine contain latex. It is essentially clear and slightly opalescent in color and 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.

[redacted]

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

Detailed mixing instructions to achieve the targeted dosage is included in the protocol-specific MOP.

2017 A/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. Antibiotics are not used in the manufacture of this vaccine. This vaccine contains no preservative (thimerosal). There is no gelatin added to this vaccine in the manufacturing process. No components of this vaccine contain latex. It is essentially clear and slightly opalescent in color and 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.

[redacted]

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

Detailed mixing instructions to achieve the targeted dosages are included in the protocol-specific MOP.

PBS Diluent

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

AS03 Adjuvant [Adjuvant System (03)]

The AS03 adjuvant is supplied as a preservative-free, oil-in-water, whitish to yellowish homogenous milky liquid emulsion presented in 3 mL Type I, single-use 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.

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 manufacturers' Investigator's Brochures for the A/H7N9 IIV and AS03 adjuvant as well as in the protocol-specific MOP.

Sterile empty vials (2-mL, 3-mL or 5-mL) 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 course 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 participating VTEU site's research pharmacist must alert the site PI and study coordinator, if the temperature fluctuates outside of the required range. In the event the temperature fluctuates outside of the required range, including accidental deep-freezing or disruption of the cold chain, the affected study product(s) must not be administered. The site PI or responsible person should immediately contact the DMID Product Support Team at DMIDProductSupportTeam@niaid.nih.gov for further instructions before any additional study vaccinations are administered. Based on the information collected, DMID and/or the manufacturer will determine whether the affected study product(s) can be used. If it cannot be used, the site will receive specific instructions on how to return the affected study product(s) to

the DMID CMS or destroy it on site. Additional instructions for quarantine and DMID contact information are provided in the protocol-specific MOP.

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

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

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

Visually inspect the 2013 and 2017 A/H7N9 IIVs, PBS diluent and AS03 adjuvant upon receipt and prior to use. If the study product(s) appear(s) to have been damaged, contaminated or discolored, contain(s) visible particulate matter, or if there are any concerns regarding the integrity, do NOT use the affected study product(s). The affected study product(s) must be quarantined at 2°C to 8°C (36°F to 46°F) and labeled as 'Do Not Use' (until further notice). The site PI or responsible person should immediately contact the DMID Product Support Team at DMIDProductSupportTeam@niaid.nih.gov and DMID Clinical Project Manager for further instructions before any additional study vaccinations are administered. Based on the information collected, DMID and/or the manufacturer will determine whether the affected study product(s) can be used. If the affected study product(s) cannot be used, the site will receive specific instructions on how to return the affected study product(s) to the DMID CMS or destroy the affected study product(s) on site. If the 2013 or 2017 A/H7N9 IIVs, PBS diluent or 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 with PBS diluent, visually inspect the A/H7N9 IIV plus PBS diluent admixture (intermediate or final mixed vial depending on treatment arm) prior to use. The A/H7N9 IIV plus PBS diluent admixture will be essentially clear and slightly opalescent in color. For those doses that must be admixed with PBS diluent and AS03 adjuvant, visually inspect the A/H7N9 IIV/PBS diluent plus AS03 adjuvant admixture (final mixed vial) prior to use. The A/H7N9 IIV/PBS diluent plus AS03 adjuvant admixture will be milky (whitish to yellowish) in color. If the admixture(s) appear(s) to have been damaged, contaminated or discolored, contain(s) visible particulate matter, or if there are any concerns regarding the integrity, do NOT use the affected admixture(s). The affected admixture(s) must be quarantined at 2°C to 8°C (36°F to 46°F) for the A/H7N9 IIV plus PBS diluent admixture or room

temperature for the A/H7N9 IIV/PBS diluent plus AS03 adjuvant and labeled as 'Do Not Use' (until further notice). The site PI or responsible person should immediately contact the DMID Product Support Team at DMIDProductSupportTeam@niaid.nih.gov and DMID 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 admixture(s) can be used. If the affected admixture(s) cannot be used, the site will receive specific instructions on how to send the affected admixture(s) to the DMID CMS or destroy the affected admixture(s) on site. If the affected admixture is unusable, the participating VTEU site's research pharmacist will prepare another admixture. Additional instructions for quarantine and DMID contact information are provided in the protocol-specific MOP.

For those doses that must be admixed with PBS diluent, the A/H7N9 IIV plus PBS diluent admixture (intermediate or final mixed vial depending on treatment arm), once mixed, must be stored at 2°C to 8°C (36°F to 46°F) in an upright position and must be used within 8 hours. For those doses that must be admixed with PBS diluent and AS03 adjuvant, the A/H7N9 IIV/PBS diluent plus AS03 adjuvant admixture (final mixed vial), once mixed, must be stored at room temperature in an upright position and must be used within 8 hours.

Only one- 0.5 mL dose of study vaccine should be withdrawn from the intermediate and final mixed vial(s). Gently invert the intermediate and final mixed vial(s) 5 to 7 times immediately before the single 0.5 mL dose of study vaccine is withdrawn. **Do not shake the intermediate and final mixed vial(s).**

Study vaccine administration to the subject will be performed by an unblinded study personnel member who is credentialed to administer vaccines and may also participate in dose preparation, but will not be involved in study-related assessments or have subject contact for data collection following study vaccine administration to the subject. One- 0.5 mL dose of study vaccine will be administered to the subject via a single IM injection into the deltoid muscle of the subject's preferred arm on the day of study vaccine administration to the subject. See the protocol-specific MOP for information on how to administer IM injections. The site of injection (right or left arm) and time of study vaccine administration to the subject will be recorded on the appropriate DCF. Study vaccinations subsequent to the first study vaccination may be given in the same preferred arm as long as there is no interference with the reactogenicity assessment.

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 1-mL disposable, sterile syringe. 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.

6.3 Modification of Study Intervention/Investigational Product for a Subject

There will be no dose modifications. If a subject's second study vaccination is deferred, it should be rescheduled to occur within the acceptable protocol-specified window for the Dose 2 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 2013 and 2017 A/H7N9 IIVs, PBS diluent, AS03 adjuvant, and sterile empty vials, the site PI is responsible for study product distribution and disposition, and has ultimate responsibility for study product accountability. The site PI may delegate to the participating VTEU site's research pharmacist responsibility for study product accountability. The participating VTEU site's 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). Study product accountability records and dispensing logs will also capture vial numbers, including intermediate and final mixed vial numbers, 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 recorded on the appropriate DCF. All study product(s), including the amount of 2013 and 2017 A/H7N9 IIVs, PBS diluent, AS03 adjuvant, and admixtures, 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 site's study product accountability records and dispensing logs per the site monitoring plan.

Used and unused vials of 2013 and 2017 A/H7N9 IIVs, PBS diluent, AS03 adjuvant, and admixtures will be retained until monitored and released for disposition, as applicable. This can occur on an ongoing basis for used vials of 2013 and 2017 A/H7N9 IIVs, PBS diluent, AS03 adjuvant, and admixtures. Used vials of 2013 and 2017 A/H7N9 IIVs, PBS diluent, AS03 adjuvant, and admixtures 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 2013 and 2017 A/H7N9 IIVs, PBS diluent, AS03 adjuvant, 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 vaccine will be administered to the subject by an unblinded study vaccine administrator via IM injection at all dosing times per the subject's randomized treatment assignment and as described in Section 6.2. Thus, subject compliance is not anticipated to be an issue. Deviations from the dose schedule may only occur as described in Section 6.3. Study vaccine administration to the subject will be recorded on the appropriate DCF.

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 any non-study influenza vaccines will be solicited through approximately 180 days after the last study vaccination, and reported in the eCRF. Use of a new medication should prompt evaluation for the occurrence of any MAAE, including a new diagnosis of chronic medical disease or condition.

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

7 STUDY PROCEDURES/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 clinic visits after the first study vaccination, an interim medical history will be obtained by interview of subjects and any changes since the previous clinic visit or phone call will be noted. 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 on Day 1 prior to the first study vaccination, a physical examination will be performed on all subjects, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator, to include the following organs and organ systems: skin, head and neck, lungs, heart, liver, spleen, extremities, lymph nodes, and nervous system, and as an assessment for signs suggestive of PIMMCs. At follow-up clinic visits after the first study vaccination, a targeted physical examination may be performed, if indicated based on the subject's interim medical history, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator. Targeted physical examinations should also include an assessment for signs suggestive of PIMMCs.

Vital signs (oral temperature, pulse and blood pressure [BP]) will be collected at the screening visit (optional) and prior to each study vaccination. Vital signs assessed on Day 1 prior to the first study vaccination will be considered as baseline. Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature.

Height and weight will be collected 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 7 days 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 immediately prior to each study vaccination to establish baseline, then the study vaccination will be given.

Subjects will be observed in the clinic for at least 20 minutes after each study vaccination. The study vaccination site will be examined, post-administration reactogenicity assessments will be performed, and any AE/SAEs will be recorded on the appropriate DCF prior to discharge from the clinic. The study vaccination site will also be examined approximately 1, 3 and 7 days after each study vaccination.

All subjects will complete a Memory Aid from the time of each study vaccination through 7 days after each study vaccination. Memory Aids will be reviewed with the subjects for any AEs (solicited injection site and systemic reactions as well as unsolicited AEs), SAEs and concomitant medications (including solicitation for receipt of any non-study influenza vaccines) approximately 1, 3 and 7 days after each study vaccination via phone call or clinic visit.

7.2 Laboratory Evaluations

Clinical laboratory evaluations and special assays are described below. Refer also to Sections 4 and 8 as well as Appendix A: Schedule of Study Procedures and Evaluations and Appendix B: Schedule of Special Assays.

7.2.1 Clinical Laboratory Evaluations

Urine or serum pregnancy tests will be performed locally by the site at the screening visit (optional) and within 24 hours prior to each study vaccination for 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.

The ESR evaluation will be performed locally by the site at the screening visit (optional) or on Day 1 prior to the first study vaccination. Results must be known prior to randomization on Day 1 and administration of the first study vaccination, and confirmed as less than 30 mm per hour to be eligible for participation in this trial and receipt of the first study vaccination.

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

The volume of venous blood to be collected for ESR and clinical safety laboratory evaluations is presented in Table 4 and 5.

7.2.2 Special Assays or Procedures

Serological Assays

Once the last subject completes the visits that occur through approximately 21 days after the last study vaccination, serum specimens collected for these visits will be shipped from the DMID CMS to specified research laboratories for serological analysis. Once the last subject completes the visit that occurs approximately 180 days after the last study vaccination, serum specimens collected for this visit will be shipped from the DMID CMS to specified research laboratories to conduct the final serological analyses.

HAI and Neut Antibody Assays

Assays to determine serum levels of HAI and Neut antibodies will be performed by Southern Research on specimens collected at multiple time points prior to and following each study vaccination. Subjects who withdraw early will have these assays run on available sera.

HA Stem-Specific Assays

Assays to determine and quantitate HA stem-specific antibodies are in development, and the specified research laboratories for this assessment are to be determined. It is anticipated that serum levels of anti-HA stem-specific antibodies will be determined from specimens collected at multiple time points prior to and following each study vaccination. Subjects who withdraw early will have these assays run on available sera.

NA-Specific Assays

Assays to determine the NA content and NAI antibodies are in development, and the specified research laboratories for this assessment is to be determined. The correlation of the NA content in the 2013 and 2017 A/H7N9 IIVs with the elicited N9 NA-specific serum antibody responses

may be determined from specimens collected at multiple time points prior to and following each study vaccination.

Any research laboratory involved with the determination of NA content or N9 NA-specific serum antibody responses will remain blinded to the results from the HAI and Neut antibody assays performed by Southern Research.

Cellular Immunology Assays

This clinical trial will also investigate novel methods for identifying and assessing alternative cellular correlates of protection against influenza infection at multiple time points following each study vaccination. These will include longitudinal assessments of: 1) the kinetics, magnitude, specificity, and/or quality of influenza-specific B and T cells, cT_{FH} cells and innate immune cells (monocytes, DCs and NK cells); 2) the frequency of influenza-specific IgA, IgG and IgM plasmablasts (ASCs); and 3) B cell receptor somatic hypermutation and repertoire assessments.

Given the requirement for freshly isolated PBMCs, the plasmablast assay will be performed only on specimens collected from subjects enrolled at the specified site(s), which will perform the plasmablast assay. All other frozen PBMCs will be shipped from the DMID CMS to specified research laboratories for cellular immunology analyses. Residual plasma specimens collected during the processing of PBMCs may be frozen and shipped to the DMID CMS.

Venous blood will also be collected at multiple time points following each study vaccination for the future research use of serum, plasma and PBMCs.

The volume of venous blood to be collected for serological and cellular immunology assays as well as future research is presented in Table 4 and 5. Note: There are two different dosing intervals between the priming (first) and boosting (second) doses (21 days vs. 4 months). Treatment Arms 1 and 4 receive study vaccinations on Days 1 and 22; and Treatment Arms 2, 3, 5, and 6 receive study vaccinations on Days 1 and 121.

Table 4: Venipuncture Volumes for Treatment Arms 1 and 4

Study Visit Number	**V00**	**V01**	**V02**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08**	**V09**	**V10**	**V11**	**V13**	**V15**	**Cumulative Blood Volume Total (mL)**
Study Day post first study vaccination	**Screening (Optional) D-28 to -1**	**Enrollment Dose 1 D1**	**D2+1d**	**D4+1d**	**D8-1/+2d**	**D15±1d**	**D22+7d**	***D23***	***D25***	***D29***	***D36***	***D43***	***D112***	***D202***	
Study Day post second study vaccination							**Dose 2 D1**	**D2+1d**	**D4+1d**	**D8-1/+2d**	**D15±1d**	**D22+7d**	**D91±14d**	**D181±14d**	
Study Procedure/Evaluation															
Study Vaccination		X					X								
ESR	4^	–^*													**4**
Clinical Safety Laboratory Evaluations~		10#†			10		10†			10					**40**
Serological Assays		15†					15†					15		15	**60**
Cellular Immunology Assays		64†	4	8	44	8	32†	4	8	44	8		40	32	**296**
Future Research		16†	16	16	21	16	16†	16	16	21	16	16	16	16	**218**
Per Visit Blood Volume Total (mL)	**4**	**105**	**20**	**24**	**75**	**24**	**73**	**20**	**24**	**75**	**24**	**31**	**56**	**63**	**618**
Running Blood Volume Total (mL)	**4**	**109**	**129**	**153**	**228**	**247**	**320**	**340**	**364**	**444**	**458**	**489**	**545**	**618**	

^ Drawn up to 28 days prior to the first study vaccination. The ESR value must be confirmed as less than 30 mm per hour prior to randomization and first study vaccination.

* Not required if done at the optional screening visit.

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

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

† Blood must be drawn immediately prior to study vaccination.

Table 5: Venipuncture Volumes for Treatment Arms 2, 3, 5, and 6

Study Visit Number	**V00**	**V01**	**V02**	**V03**	**V04**	**V05**	**V06**	**V08**	**V09**	**V10**	**V11**	**V12**	**V13**	**V15**	**V17**	**Cumulative Blood Volume Total (mL)**
Study Day post first study vaccination	**Screening (Optional) D-28 to -1**	**Enrollment Dose 1 D1**	**D2+1d**	**D4+1d**	**D8-1/+2d**	**D15±1d**	**D22+7d**	**D121-7/+14d**	***D122***	***D124***	***D128***	***D135***	***D142***	***D211***	***D301***	
Study Day post second study vaccination								**Dose 2 D1**	**D2+1d**	**D4+1d**	**D8-1/+2d**	**D15±1d**	**D22+7d**	**D91±14d**	**D181±14d**	
Study Procedure/Evaluation																
Study Vaccination		X						X								
ESR	4^	–^*														**4**
Clinical Safety Laboratory Evaluations~		10#†			10			10†			10					**40**
Serological Assays		15†					15	15†					15		15	**75**
Cellular Immunology Assays		64†	4	8	44	8		32†	4	8	44	8		40	32	**296**
Future Research		16†	16	16	21	16	16	16†	16	16	21	16	16	16	16	**234**
Per Visit Blood Volume Total (mL)	**4**	**105**	**20**	**24**	**75**	**24**	**31**	**73**	**20**	**24**	**75**	**24**	**31**	**56**	**63**	**649**
Running Blood Volume Total (mL)	**4**	**109**	**129**	**153**	**228**	**247**	**278**	**351**	**371**	**395**	**475**	**489**	**520**	**576**	**649**	

^ Drawn up to 28 days prior to the first study vaccination. The ESR value must be confirmed as less than 30 mm per hour prior to randomization and first study vaccination.

* Not required if done at the optional screening visit.

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

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

† Blood must be drawn immediately prior to study vaccination.

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 clinical 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 additional serological assays will be shipped from the participating VTEU sites to the DMID CMS, and then provided by the DMID CMS to the specified research laboratories in a blinded manner.

Specimens for cellular immunology assays using frozen PBMCs will be shipped from the participating VTEU sites to the DMID CMS, and then provided by the DMID CMS to the specified research laboratories in a blinded manner.

Specimens for the plasmablast assay using freshly isolated PBMCs will remain on site at the specified site(s).

Residual plasma specimens collected during the processing of PBMCs may be frozen and shipped to the DMID CMS.

Specimens for future research will be shipped from the participating VTEU sites to the DMID CMS.

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 as well as Appendix A: Schedule of Study Procedures and Evaluations and Appendix B: Schedule of Special Assays.

Note: There are two different dosing intervals between the priming (first) and boosting (second) doses (21 days vs. 4 months). Treatment Arms 1 and 4 receive study vaccinations on Days 1 and 22; and Treatment Arms 2, 3, 5, and 6 receive study vaccinations on Days 1 and 121.

8.1 Screening (Optional) and Enrollment Visits

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

- Subjects will be provided with a description of this trial (purpose and study procedures) and asked to read and sign the ICF. The ICF will be signed prior to performing any study procedures, including administration of the first study vaccination.
- Demographic information will be obtained by interview of subjects.
- Eligibility criteria will be reviewed with subjects to ensure eligibility.
- Complete medical history will be obtained by interview of subjects to ensure eligibility.
- All concomitant medications taken within 60 days prior to signing the ICF will be reviewed with subjects to determine stability of chronic diseases and eligibility. Medications reported in the eCRF are limited to those taken within 30 days prior to the first study vaccination.
- Subject receipt of licensed, seasonal influenza vaccine over the current (2018-2019) and previous two influenza seasons (2016-2017 and 2017-2018), 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 is not exclusionary, as long as it has been administered within the allowable window (see Section 5.1.2).
- Subject receipt of non-seasonal influenza 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. Prior receipt of non-seasonal influenza vaccine is not exclusionary, except influenza A/H7 vaccine (see Section 5.1.2).

- Vital signs, including oral temperature, pulse and BP, will be obtained to ensure eligibility. 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, and nervous system, and as an assessment for signs suggestive of PIMMCs, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.

- A urine or serum pregnancy test may be performed locally by the site for 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 to ensure eligibility.

8.1.2 Visit 01, Day 1, Enrollment (for subjects previously screened at Day -28 to -1) and First Study Vaccination (Dose 1), Clinic Visit, All Treatment Arms

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

- Eligibility criteria, including results of the ESR evaluation, will be reviewed with subjects prior to the first study vaccination to ensure continued eligibility. The ESR value must be confirmed as less than 30 mm per hour prior to randomization and first study vaccination.

- Interim medical history, including an assessment for new medical conditions, stability of chronic diseases and symptoms suggestive of PIMMCs, will be obtained by interview of subjects prior to the first study vaccination. Any changes in medical history since the screening visit will be reviewed with subjects prior to the first study vaccination to ensure continued eligibility.

- All concomitant medications (including solicitation for receipt of any non-study influenza vaccines) will be reviewed with subjects prior to the first study vaccination for accuracy and completeness. Any new concomitant medications taken since the screening visit will be reviewed with subjects prior to the first study vaccination to ensure continued

eligibility. Medications reported in the eCRF are limited to those taken within 30 days prior to the first study vaccination.

- Vital signs, including oral temperature, pulse and BP, will be obtained prior to the first study vaccination to ensure continued eligibility. Vital signs assessed on Day 1 prior to the first study vaccination will be considered as baseline. Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature.

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

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

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

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

- Approximately 15 mL of venous blood will be collected immediately prior to the first study vaccination for baseline serological assays.

- Approximately 64 mL of venous blood will be collected immediately prior to the first study vaccination for baseline cellular immunology assays.

- Approximately 16 mL of venous blood will be collected immediately prior to the first study vaccination for future research.

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

- Subjects will then receive one- 0.5 mL dose of study vaccine via a single IM injection into the deltoid muscle of the subjects' preferred arm. The site of injection (right or left

arm) and time of study vaccine administration to the subject will be recorded on the appropriate DCF. Subjects will be observed in the clinic for at least 20 minutes after the first study vaccination. The first study vaccination site will be examined, post-administration reactogenicity assessments will be performed, and any AE/SAEs will be recorded on the appropriate 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, unsolicited AEs, and concomitant medications. Subjects will be encouraged to take their oral temperature around the same time each day. Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature. Subjects will be instructed on how to use their Memory Aid and how to measure and record AEs prior to discharge from the clinic. Subjects will be instructed to notify the study center if they develop any severe reactions after the first study vaccination. If the site PI or appropriate sub-investigator deems the reaction severe enough, further instructions will be given to the subject on the proper course of action, including a return to the clinic for immediate evaluation if appropriate.

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

- Subjects will be provided with a description of this trial (purpose and study procedures) and asked to read and sign the ICF. The ICF will be signed prior to performing any study procedures, including administration of the first study vaccination.

- Demographic information will be obtained by interview of subjects prior to the first study vaccination.

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

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

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

- Subject receipt of licensed, seasonal influenza vaccine over the current (2018-2019) and

previous two influenza seasons (2016-2017 and 2017-2018), 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 is not exclusionary, as long as it has been administered within the allowable window (see Section 5.1.2).

- Subject receipt of non-seasonal influenza 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. Prior receipt of non-seasonal influenza vaccine is not exclusionary, except influenza A/H7 vaccine (see Section 5.1.2).

- Vital signs, including oral temperature, pulse and BP, will be obtained prior to the first study vaccination to ensure eligibility. Vital signs assessed on Day 1 prior to the first study vaccination will be considered as baseline. Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature.

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

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

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

- Approximately 4 mL of venous blood will be collected for ESR, and performed locally by the site prior to the first study vaccination. The ESR value must be confirmed as less than 30 mm per hour prior to randomization and first study vaccination.

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

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

- Approximately 15 mL of venous blood will be collected immediately prior to the first study vaccination for baseline serological assays.

- Approximately 64 mL of venous blood will be collected immediately prior to the first study vaccination for baseline cellular immunology assays.

- Approximately 16 mL of venous blood will be collected immediately prior to the first study vaccination for future research.

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

- Subjects will then receive one- 0.5 mL dose of study vaccine via a single IM injection into the deltoid muscle of the subjects' preferred arm. The site of injection (right or left arm) and time of study vaccine administration to the subject will be recorded on the appropriate DCF. Subjects will be observed in the clinic for at least 20 minutes after the first study vaccination. The first study vaccination site will be examined, post-administration reactogenicity assessments will be performed, and any AE/SAEs will be recorded on the appropriate 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, unsolicited AEs, and concomitant medications. Subjects will be encouraged to take their oral temperature around the same time each day. Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature. Subjects will be instructed on how to use their Memory Aid and how to measure and record AEs prior to discharge from the clinic. Subjects will be instructed to notify the study center if they develop any severe reactions after the first study vaccination. If the site PI or appropriate sub-investigator deems the reaction severe enough, further instructions will be given to the subject on the proper course of action, including a return to the clinic for immediate evaluation if appropriate.

8.2 Follow-up Visits

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

8.2.1 Visit 02, Day 2, Clinic Visit, All Treatment Arms (Window: Day 2+1 day post first study vaccination)

- Interim medical history, including an assessment for new medical conditions, stability of chronic diseases and symptoms suggestive of PIMMCs, will be obtained by interview of subjects and any changes since the previous clinic visit or phone call will be noted.
- All concomitant medications (including solicitation for receipt of any non-study influenza vaccines) will be recorded on the appropriate DCF.
- All AE/SAEs will be recorded on the appropriate DCF.
- Memory Aid information will be reviewed with subjects.
- A targeted physical examination, including an assessment for signs suggestive of PIMMCs, may be performed, if indicated based on review of interim medical history, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.
- The first study vaccination site will be examined.
- Approximately 4 mL of venous blood will be collected for cellular immunology assays.
- Approximately 16 mL of venous blood will be collected for future research.

8.2.2 Visit 03, Day 4, Clinic Visit, All Treatment Arms (Window: Day 4+1 day post first study vaccination)

- Interim medical history, including an assessment for new medical conditions, stability of chronic diseases and symptoms suggestive of PIMMCs, will be obtained by interview of subjects and any changes since the previous clinic visit or phone call will be noted.
- All concomitant medications (including solicitation for receipt of any non-study influenza vaccines) will be recorded on the appropriate DCF.
- All AE/SAEs will be recorded on the appropriate DCF.
- Memory Aid information will be reviewed with subjects.
- A targeted physical examination, including an assessment for signs suggestive of PIMMCs, may be performed, if indicated based on review of interim medical history, by

a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.

- The first study vaccination site will be examined.
- Approximately 8 mL of venous blood will be collected for cellular immunology assays.
- Approximately 16 mL of venous blood will be collected for future research.

8.2.3 Visit 04, Day 8, Clinic Visit, All Treatment Arms (Window: Day 8-1/+2 days post first study vaccination)

- Interim medical history, including an assessment for new medical conditions, stability of chronic diseases and symptoms suggestive of PIMMCs, will be obtained by interview of subjects and any changes since the previous clinic visit or phone call will be noted.
- All concomitant medications (including solicitation for receipt of any non-study influenza vaccines) will be recorded on the appropriate DCF.
- All AE/SAEs will be recorded on the appropriate DCF.
- Memory Aid information will be reviewed with subjects.
- A targeted physical examination, including an assessment for signs suggestive of PIMMCs, may be performed, if indicated based on review of interim medical history, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.
- The first study vaccination site will be examined.
- Approximately 10 mL of venous blood will be collected for clinical safety labs (WBC, Hgb, PLT, ALT, T. Bili, Cr) to be performed by the central (clinical) laboratory.
- Approximately 44 mL of venous blood will be collected for cellular immunology assays.
- Approximately 21 mL of venous blood will be collected for future research.

Note: Subjects that complete this visit on Day 7 will be reminded to complete their Memory Aid through the end of Day 8, and study personnel will contact these subjects by phone to review their Memory Aid information and solicit any AE/SAEs and concomitant medications (including solicitation for receipt of any non-study influenza vaccines). Based on the information collected, subjects may be asked to return to the clinic for evaluation.

8.2.4 Visit 05, Day 15, Clinic Visit, All Treatment Arms (Window: Day 15±1 day post first study vaccination)

- Interim medical history, including an assessment for new medical conditions, stability of chronic diseases and symptoms suggestive of PIMMCs, will be obtained by interview of subjects and any changes since the previous clinic visit or phone call will be noted.
- All concomitant medications (including solicitation for receipt of any non-study influenza vaccines) 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 PI or sub-investigator.
- Approximately 8 mL of venous blood will be collected for cellular immunology assays.
- Approximately 16 mL of venous blood will be collected for future research.

8.2.5 Clinic Visit, Treatment Arms 2, 3, 5, and 6

Visit 06, Day 22 (Window: Day 22+7 days post first study vaccination), Treatment Arms 2, 3, 5, and 6

- 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 phone call will be noted.
- All concomitant medications (including solicitation for receipt of any non-study influenza vaccines) 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 PI or sub-investigator.
- Approximately 15 mL of venous blood will be collected for serological assays.

- Approximately 16 mL of venous blood will be collected for future research.

8.2.6 Safety Follow-up, Phone Call, Treatment Arms 2, 3, 5, and 6

Visit 07, Day 61 (Window: Day 61±7 days post first study vaccination), Treatment Arms 2, 3, 5, and 6

Subjects will be contacted by phone to query for safety events and concomitant medications (including solicitation for receipt of any non-study influenza vaccines). AEs limited to SAEs and MAAEs, including NOCMCs and PIMMCs, that have occurred since the previous clinic visit or phone call will be solicited. Based on the information collected, subjects may be asked to return to the clinic for evaluation.

8.2.7 Second Study Vaccination (Dose 2), Clinic Visit, All Treatment Arms

Visit 06, Day 22 (Window: Day 22+7 days post first study vaccination), Treatment Arms 1 and 4

Visit 08, Day 121 (Window: Day 121-7/+14 days post first study vaccination), Treatment Arms 2, 3, 5, and 6

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

- For a subject to receive the second study vaccination, refer to Section 5.2.3 for additional second study vaccination eligibility criteria.

- Interim medical history, including an assessment for new medical conditions, stability of chronic diseases and symptoms suggestive of PIMMCs, will be obtained by interview of subjects prior to the second study vaccination. Any changes in medical history since the first study vaccination will be reviewed with subjects prior to the second study vaccination to ensure continued eligibility.

- All concomitant medications (including solicitation for receipt of any non-study influenza vaccines) will be recorded on the appropriate DCF prior to the second study vaccination. Any new concomitant medications taken since the first study vaccination will be reviewed with subjects prior to the second study vaccination to ensure continued eligibility.

- All AE/SAEs will be recorded on the appropriate DCF prior to the second study vaccination. Note: AEs will be limited to SAEs and MAAEs, including NOCMCs and

PIMMCs, for subjects who are discontinued from receipt of the second study vaccination and being followed for safety.

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

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

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

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

- Approximately 15 mL of venous blood will be collected immediately prior to the second study vaccination for serological assays.

- Approximately 32 mL of venous blood will be collected immediately prior to the second study vaccination for cellular immunology assays.

- Approximately 16 mL of venous blood will be collected immediately prior to the second study vaccination for future research.

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

- Subjects will then receive one- 0.5 mL dose of study vaccine via a single IM injection into the deltoid muscle of the subjects' preferred arm. The second study vaccination may be given in the same preferred arm as long as there is no interference with the reactogenicity assessment. The site of injection (right or left arm) and time of study vaccine administration to the subject will be recorded on the appropriate DCF. Subjects will be observed in the clinic for at least 20 minutes after the second study vaccination.

The second study vaccination site will be examined, post-administration reactogenicity assessments will be performed, and any AE/SAEs will be recorded on the appropriate 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, unsolicited AEs, and concomitant medications. Subjects will be encouraged to take their oral temperature around the same time each day. Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature. Subjects will be instructed on how to use their Memory Aid and how to measure and record AEs prior to discharge from the clinic. Subjects will be instructed to notify the study center if they develop any severe reactions after the second study vaccination. If the site PI or appropriate sub-investigator deems the reaction severe enough, further instructions will be given to the subject on the proper course of action, including a return to the clinic for immediate evaluation if appropriate.

8.2.8 Clinic Visit, All Treatment Arms

Visit 07, Day 23 (Window: Day 2+1 day post second study vaccination), Treatment Arms 1 and 4

Visit 09, Day 122 (Window: Day 2+1 day post second study vaccination), Treatment Arms 2, 3, 5, and 6

- 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 phone call will be noted.

- All concomitant medications (including solicitation for receipt of any non-study influenza vaccines) will be recorded on the appropriate DCF.

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

- Memory Aid information will be reviewed with subjects.

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

- The second study vaccination site will be examined.
- Approximately 4 mL of venous blood will be collected for cellular immunology assays.
- Approximately 16 mL of venous blood will be collected for future research.

8.2.9 Clinic Visit, All Treatment Arms

Visit 08, Day 25 (Window: Day 4+1 day post second study vaccination), Treatment Arms 1 and 4

Visit 10, Day 124 (Window: Day 4+1 day post second study vaccination), Treatment Arms 2, 3, 5, and 6

- 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 phone call will be noted.
- All concomitant medications (including solicitation for receipt of any non-study influenza vaccines) will be recorded on the appropriate DCF.
- All AE/SAEs will be recorded on the appropriate DCF. Note: AEs will be limited to SAEs and MAAEs, including NOCMCs and PIMMCs, for subjects who are discontinued from receipt of the second study vaccination and being followed for safety.
- Memory Aid information will be reviewed with subjects.
- A targeted physical examination, including an assessment for signs suggestive of PIMMCs, may be performed, if indicated based on review of interim medical history, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.
- The second study vaccination site will be examined.
- Approximately 8 mL of venous blood will be collected for cellular immunology assays.
- Approximately 16 mL of venous blood will be collected for future research.

8.2.10 Clinic Visit, All Treatment Arms

Visit 09, Day 29 (Window: Day 8-1/+2 days post second study vaccination), Treatment Arms 1 and 4

Visit 11, Day 128 (Window: Day 8-1/+2 days post second study vaccination), Treatment Arms 2, 3, 5, and 6

- 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 phone call will be noted.
- All concomitant medications (including solicitation for receipt of any non-study influenza vaccines) will be recorded on the appropriate DCF.
- All AE/SAEs will be recorded on the appropriate DCF. Note: AEs will be limited to SAEs and MAAEs, including NOCMCs and PIMMCs, for subjects who are discontinued from receipt of the second study vaccination and being followed for safety.
- Memory Aid information will be reviewed with subjects.
- A targeted physical examination, including an assessment for signs suggestive of PIMMCs, may be performed, if indicated based on review of interim medical history, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-investigator.
- The second study vaccination site will be examined.
- Approximately 10 mL of venous blood will be collected for clinical safety labs (WBC, Hgb, PLT, ALT, T. Bili, Cr) to be performed by the central (clinical) laboratory.
- Approximately 44 mL of venous blood will be collected for cellular immunology assays.
- Approximately 21 mL of venous blood will be collected for future research.

Note: Subjects that complete this visit on Day 7 will be reminded to complete their Memory Aid through the end of Day 8, and study personnel will contact these subjects by phone to review their Memory Aid information and solicit any AE/SAEs and concomitant medications (including solicitation for receipt of any non-study influenza vaccines). Based on the information collected, subjects may be asked to return to the clinic for evaluation.

8.2.11 Clinic Visit, All Treatment Arms

Visit 10, Day 36 (Window: 15±1 day post second study vaccination), Treatment Arms 1 and 4

Visit 12, Day 135 (Window: Day 15±1 day post second study vaccination), Treatment Arms 2, 3, 5, and 6

- 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 phone call will be noted.
- All concomitant medications (including solicitation for receipt of any non-study influenza vaccines) will be recorded on the appropriate DCF.
- All AE/SAEs will be recorded on the appropriate DCF. Note: AEs will be limited to SAEs and MAAEs, including NOCMCs and PIMMCs, for subjects who are discontinued from receipt of the second study vaccination and 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 PI or sub-investigator.
- Approximately 8 mL of venous blood will be collected for cellular immunology assays.
- Approximately 16 mL of venous blood will be collected for future research.

8.2.12 Clinic Visit, All Treatment Arms

Visit 11, Day 43 (Window: Day 22+7 days post second study vaccination), Treatment Arms 1 and 4

Visit 13, Day 142 (Window: Day 22+7 days post second study vaccination), Treatment Arms 2, 3, 5, and 6

- 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 phone call will be noted.
- All concomitant medications (including solicitation for receipt of any non-study influenza vaccines) will be recorded on the appropriate DCF.

- All AE/SAEs will be recorded on the appropriate DCF. Note: AEs will be limited to SAEs and MAAEs, including NOCMCs and PIMMCs, for subjects who are discontinued from receipt of the second study vaccination and 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 PI or sub-investigator.

- Approximately 15 mL of venous blood will be collected for serological assays.

- Approximately 16 mL of venous blood will be collected for future research.

8.2.13 Safety Follow-up, Phone Call, All Treatment Arms

Visit 12, Day 82 (Window: Day 61±7 days post second study vaccination), Treatment Arms 1 and 4

Visit 14, Day 181 (Window: Day 61±7 days post second study vaccination), Treatment Arms 2, 3, 5, and 6

Subjects will be contacted by phone to query for safety events and receipt of any non-study influenza vaccines. AEs limited to SAEs and MAAEs, including NOCMCs and PIMMCs, that have occurred since the previous clinic visit or phone call will be solicited. Based on the information collected, subjects may be asked to return to the clinic for evaluation.

8.2.14 Clinic Visit, All Treatment Arms

Visit 13, Day 112 (Window: Day 91±14 days post second study vaccination), Treatment Arms 1 and 4

Visit 15, Day 211 (Window: Day 91±14 days post second study vaccination), Treatment Arms 2, 3, 5, and 6

- 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 phone call will be noted.

- Receipt of any non-study influenza vaccines will be recorded on the appropriate DCF.

- AEs limited to SAEs and MAAEs, including NOCMCs and PIMMCs, that have occurred since the previous clinic visit or phone call will be solicited.

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

- Approximately 40 mL of venous blood will be collected for cellular immunology assays.

- Approximately 16 mL of venous blood will be collected for future research.

8.2.15 Safety Follow-up, Phone Call, All Treatment Arms

Visit 14, Day 142 (Window: Day 121±14 days post second study vaccination), Treatment Arms 1 and 4

Visit 16, Day 241 (Window: Day 121±14 days post second study vaccination), Treatment Arms 2, 3, 5, and 6

Subjects will be contacted by phone to query for safety events and receipt of any non-study influenza vaccines. AEs limited to SAEs and MAAEs, including NOCMCs and PIMMCs, that have occurred since the previous clinic visit or phone call will be solicited. Based on the information collected, subjects may be asked to return to the clinic for evaluation.

8.2.16 Clinic Visit, All Treatment Arms

Visit 15, Day 202 (Window: Day 181±14 days post second study vaccination), Treatment Arms 1 and 4

Visit 17, Day 301 (Window: Day 181±14 days post second study vaccination), Treatment Arms 2, 3, 5, and 6

- 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 phone call will be noted.

- Receipt of any non-study influenza vaccines will be recorded on the appropriate DCF.

- AEs limited to SAEs and MAAEs, including NOCMCs and PIMMCs, that have occurred since the previous clinic visit or phone call will be solicited.

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

- Approximately 15 mL of venous blood will be collected for serological assays.
- Approximately 32 mL of venous blood will be collected for cellular immunology assays.
- Approximately 16 mL of venous blood will be collected for future research.

8.3 Final Visit

8.3.1 Safety Follow-up, Phone Call, All Treatment Arms

Visit 16, Day 387 (Window: Day 366±14 days post second study vaccination), Treatment Arms 1 and 4

Visit 18, Day 486 (Window: Day 366±14 days post second study vaccination), Treatment Arms 2, 3, 5, and 6

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

8.4 Early Termination Visit (if needed)

The following activities will be performed at the Early Termination Visit on subjects who withdraw, or are withdrawn or terminated from this trial:

- Interim medical history, including an assessment for new medical conditions, 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 phone call will be noted.
- All concomitant medications will be recorded on the appropriate DCF (if prior to 21 days after the last study vaccination). Receipt of any non-study influenza vaccines will also be recorded on the appropriate DCF (if within 180 days after the last study vaccination).
- All AE/SAEs will be recorded on the appropriate DCF. AEs limited to SAEs and MAAEs, including NOCMCs and PIMMCs, that have occurred since the previous clinic visit or phone call will be solicited (if after 21 days after the last study vaccination).
- Memory Aid information will be reviewed with subjects (if within 7 days after the last study vaccination).

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

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

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

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

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

- Approximately 15 mL of venous blood will be collected for serological assays (if within 21 days after the last study vaccination).

- Approximately 24 mL of venous blood will be collected for cellular immunology assays (if within 21 days after the last study vaccination).

- Approximately 16 mL of venous blood will be collected for future research (if within 21 days after the last study vaccination).

8.5 Unscheduled Visit (if needed)

An Unscheduled Visit 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, 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 phone call will be noted (if indicated).

- All concomitant medications will be recorded on the appropriate DCF (if prior to 21 days after the last study vaccination). Receipt of any non-study influenza vaccines will also be recorded on the appropriate DCF (if within 180 days after the last study vaccination).

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

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

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

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

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

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

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

- Approximately 15 mL of venous blood will be collected for serological assays (if within 21 days after the last study vaccination).

- Approximately 24 mL of venous blood will be collected for cellular immunology assays (if within 21 days after the last study vaccination).

- Approximately 16 mL of venous blood will be collected for future research (if within 21 days after the last study 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 GCP defines an AE as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to the study treatment. The FDA defines an AE as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational)

product. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study recipient presenting for medical care, or upon review by a study monitor.

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

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

AEs must be assessed for severity and 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 entered into the eCRF.

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

New-Onset Chronic Medical Conditions (NOCMCs): NOCMCs are defined as any new ICD-10 diagnosis (10th revision of the International Statistical Classification of Diseases and Related Health Problems) that is applied to the subject during the course 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.

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

Severity of Event: AEs will be assessed by a licensed study physician listed on the Form FDA 1572 as the site PI or 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 physician'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 injection site and systemic (subjective and quantitative) reactions:

Table 6: Injection Site Reactogenicity Grading

Injection Site Reaction	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Pain – experienced without touching the injection site (spontaneous discomfort)	Subject is aware of pain, but it does not interfere with daily activity, **and** if pain medication is used, it is Over the Counter (OTC) and used for less than 24 hours	Subject is aware of pain; there is interference with daily activity **or** OTC pain medication is used for more than 24 hours	Subject is aware of pain, **and** it prevents daily activity or pain requires prescription medication
Tenderness – hurts only when injection site is touched or the arm is moved	The area immediately surrounding the injection site hurts only when touched or with arm motion, **and** it does **not** interfere with daily activity	The area immediately surrounding the injection site hurts when touched or with arm motion, **and** it interferes with daily activity	The area immediately surrounding the injection site hurts when touched or with arm motion, **and** it prevents daily activity
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:

Table 7: Injection Site Reactogenicity Measurements

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

* Will not be used as halting criteria.

Table 8: 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
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:

Table 9: Quantitative Systemic (Oral Temperature) Reactogenicity Grading

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

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

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

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

9.2.3 Additional Adverse Event Severity Grading

Pulse and BP[#] will be graded as follows:

Table 10: Pulse and BP Adverse Event Grading

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

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

Table 11: Clinical Safety Laboratory Adverse Event Grading

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
WBC $10^3/\mu L$ (Decrease)	2.5 – 3.9	1.5 – 2.4	<1.5
WBC $10^3/\mu L$ (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 $10^3/\mu L$ (Decrease)	125 – 139	100 – 124	<100
Platelets $10^3/\mu L$ (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 safety 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 PI (or appropriate sub-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 PI (or appropriate sub-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 or alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 as the site PI or sub-investigator.
- Recorded on the appropriate SAE form and entered into the eCRF.

- Followed through resolution by a licensed study physician listed on the Form FDA 1572 as the site PI or sub-investigator.

- Reviewed and evaluated by the Independent Safety Monitor (ISM) (as deemed necessary), DSMB (periodic review unless related), DMID, and IRB.

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

The site PI or appropriate sub-investigator is responsible for recording all AE/SAEs that are observed or reported during this trial, regardless of 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 subject safety and protocol conduct.

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

9.3.2 Regulatory Reporting for Studies Conducted Under DMID-Sponsored IND

Following notification from the site PI or appropriate sub-investigator, DMID, the Investigational New Drug (IND) sponsor, will report any suspected adverse reaction that is both serious and unexpected. DMID will report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the AE. DMID will notify the FDA and all investigators (i.e., all participating VTEU site PIs to whom the sponsor is providing drug under its IND(s) or under any PI's IND(s)) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting as specified in 21 CFR Part 312.32. DMID will also notify the 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 the FDA, DMID will submit to the FDA any additional data or information that the agency deems

necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

All 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 subjects will be recorded on the Pregnancy Report DCF. No further study vaccinations will be administered to pregnant subjects, but with the subject's permission, a venous blood sample for serological assays approximately 21 and 180 days after the last study vaccination will be obtained, and the subject will continue to be followed for safety for the duration of the prescribed safety follow-up period. 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 and entered into the eCRF.

9.5 Halting Rules

Additional enrollment and study interventions/administration of study products in this trial 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 that is considered 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 after administration of study product that is considered related to study product.

- Any subject experiences acute weakness of limbs and/or cranial nerve innervated muscles (description of potential signal of GBS) after administration of study product.

- Any subject develops a PIMMC after administration of study product.

This trial will also be halted for DSMB review/recommendation if, within 7 days after administration of either study vaccination, any of the following occurs:

- 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 study vaccine administrations, across all treatment arms, 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 study vaccine administrations, across all treatment arms, 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 study vaccine administrations, across all treatment arms, 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 study vaccine administrations, across all treatment arms, 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 products during this 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)

An ISM is a physician with relevant expertise whose primary responsibility is to provide to DMID an independent safety assessment in a timely fashion. This is a voluntary position that does not receive payment. The ISM must meet the requirements of the NIAID Conflict of Interest (COI) policy.

For this clinical trial an ISM is <u>not</u> required. However, at each participating VTEU site, **upon DMID Medical Monitor request**, the site PI will identify a physician with relevant expertise, to act as a Secondary Medical Assessor (SMA). The SMA will examine a subject and/or medical records and provide to DMID a medical assessment (or second medical opinion) of the safety event in question. The site PI or appropriate sub-investigator will send to the DMID Medical Monitor, a summary of the event and include the site PI or appropriate sub-investigator and SMA assessments.

Note: In the case that DMID has requested this type of evaluation multiple times, DMID may request the participating VTEU site(s) identify an ISM to assist DMID with safety oversight, and then the below requirements will apply.

The ISM:

- Is in close proximity to the study site and has the authority and ability to readily access subject records in real time.
- May be a member of the participating VTEU site's staff, but preferably be from a different organizational group within the institution.
- Should <u>not</u> be in a direct supervisory relationship with the site PI.

- Should have no direct involvement in the conduct of the study.

The ISM will:

- Sign a COI certification at the time he/she is asked to participate and provide updates to this information as needed.
- Receive reports of SAEs from the site PI or appropriate sub-investigator and will be notified by email when DMID is notified of the SAE.
- Evaluate the SAE and report his/her clinical assessment to DMID in a timely manner.
- Communicate with the site PI or appropriate sub-investigator at the participating VTEU site as needed.
- Review additional safety related events at the request of DMID.
- Provide additional information to DMID and/or the DSMB by teleconference as requested.

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 COI 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. 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 subject, clinical, safety, reactogenicity, and immunogenicity 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. The DSMB will review SAEs on a regular basis and ad hoc during this trial. The DMID Medical Monitor and the ISM (as deemed necessary) will be responsible for reviewing SAEs in real time.

The DSMB will conduct the following reviews:

- Data review for safety at trial-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 subjects.

- Data review when 8-day reactogenicity and clinical safety laboratory data following the first study vaccination is available for 75% of study subjects.

- Ad hoc when a halting rule is met, or DMID/DSMB chair may convene an ad hoc meeting if there are immediate concerns regarding observations during the course of this trial. The DMID Medical Monitor is empowered to stop enrollment and study vaccinations if AEs that meet the halting criteria are reported.

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

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

10 CLINICAL MONITORING

10.1 Site Monitoring Plan

Site monitoring is conducted to ensure that the human subjects' protections, study and laboratory procedures, study interventions/administration of study products, and data collection processes are of high quality and meet sponsor and ICH E6 GCP guidelines and applicable federal 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. DMID-designated clinical monitors will verify that this trial is conducted and data are generated, documented (recorded) and reported in compliance with the protocol, ICH E6 GCP guidelines and applicable regulatory requirements. Clinical monitoring reports will be submitted to DMID.

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 PIs 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, 19 to 50 years of age, the safety, reactogenicity and immunogenicity of one or two doses 2013 and 2017 A/H7N9 IIVs, administered intramuscularly at different dosages (3.75 or 15 mcg of hemagglutinin (HA) per dose), given with or without AS03 adjuvant, using different heterologous and homologous prime-boost vaccination schedules. These treatment arms are included to allow evaluation of the study vaccine dosage, study vaccination schedule and potential of the adjuvant to enhance the immune response to the 2013 and 2017 A/H7N9 IIVs. Additional goals are to investigate novel methods for identifying and assessing alternative cellular correlates of protection against influenza infection.

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 by this vaccine and to uncover any safety issues that occur at a sufficiently high rate that they might be observed in a study of this size. The sample size facilitates formal testing of selected hypotheses as discussed in Section 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 outlined in Section 3.2.

11.4 Sample Size Considerations

Please refer to Study Design outlined in Section 4.

11.4.1 Study Population

The study population for this clinical trial includes males and non-pregnant females, 19 to 50 years of age, who are in good health and meet all eligibility criteria. The subjects will be recruited from the general population at each of 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, 7 VTEUs recruited 388 healthy subjects, 19 to 64 years of age, in 14 weeks. Prior experience suggests up to 15% of subjects (approximately 10% of subjects assigned to the 4-month interval and 5% of subjects assigned to the 21-day interval), 19 to 64 years of age, may be excluded from the per protocol (PP) analysis for the primary immunogenicity outcome either because they did not receive the second study vaccination, were lost-to-follow-up, or because they had a protocol deviation requiring their exclusion from the PP 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 up to 180 subjects. The sample size for this study was selected to obtain preliminary estimates in a time critical manner. While this study is not designed to test any specific null hypothesis, the following illustrates the precision and power that are available for select estimates and comparisons of interest.

Table 12 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 in the trial as a whole (N=180).

Table 12: Power (%) to Detect Safety Events

Event Frequency	N=30	N=180
≥10% Very Common	95	>99
≥1% Common	26	83
≥0.1% Uncommon	2	16
≥0.01% Rare	<1	1

Binomial confidence intervals (CI) are widest (have the least precision) when the response rate is 50%. Table 13 is presented to indicate the worst-case scenario for precision of observed exact (Clopper-Pearson) binomial confidence intervals.

Table 13: Precision of Binomial Confidence Intervals

N	95% CI
30	31-69
180	42-58

Table 14 illustrates the minimum detectable differences in the proportion of subjects responding (e.g. attaining seroconversion or a titer ≥1:40) between any two treatment arms (N=30) using a two-sided Likelihood Ratio Test and alpha = 0.05. It is assumed that up to 10% of subjects (N=3) will be excluded from the per protocol analysis. Seroconversion rates of 10% to 50% are considered.

Table 14: Minimum Detectable Difference in Proportion Responders

N per Group	Proportion Responders in Comparator Group A	80% Power	
		Minimal Detectable Difference	Proportion Responders in Comparator Group B
N=27	0.10	0.32	0.42
	0.20	0.35	0.55
	0.30	0.38	0.68
	0.40	0.37	0.77
	0.50	0.34	0.84

11.5 Planned Interim Analyses

A DSMB will be convened by DMID to review study progress and subject, clinical, safety, reactogenicity, and immunogenicity data as described in Section 9.6.2.

A set of "topline" immunogenicity and safety tables produced on an expedited timeline will be prepared as described in Section 11.6; though this report will be released while subjects remain in this trial for long-term safety follow-up, it will be considered the final analysis of these data.

Emergent public health needs may dictate additional interim safety, reactogenicity and/or immunogenicity analyses be performed on available information at any time during this trial. If this occurs, immunogenicity data will be analyzed as results are available from Southern Research.

Interim analyses will be used only 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.

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. The DSMB may also be provided with expected and observed rates of the expected AEs in an unblinded fashion, and may request the treatment assignment be unblinded for an individual subject if required for safety assessment. The DSMB will review grouped and unblinded data in the closed session only. The DSMB will meet and review this data at trial-specific time frames 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.

The interim safety reports generated for the DSMB are not intended to be published; they will be used only for informing emergency preparedness.

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

Should emergent public health needs dictate interim immunogenicity review, immune responses will be summarized in terms of strain-specific 2013 and 2017 A/H7N9 HAI and Neut antibody titers and the relationship to study vaccine dosage, adjuvant use and study vaccination schedule. It is anticipated that all analyses will be carried out in parallel for both assays, but reports may be prepared separately for HAIs 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, DMID Clinical Project Manager and DSMB. Reports will include data summarized by unblinded

treatment arm, but the presentation will be in a format that prevents inadvertent unblinding of any individual subject.

There is no plan to halt this trial prior to full enrollment and completion of all follow-up visits based on any interim immunogenicity results.

11.6 Final Analysis Plan

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

Analysis of exploratory immunogenicity endpoints, including cellular immunology and additional serological assays, 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 to unblinding for any analysis, which defines the analyses to be included in the topline tables and 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 HAI and Neut antibody assays for which valid results were reported. For analyses using the mITT population, subjects will be grouped based on their randomized treatment arm.

The PP population includes all subjects in the mITT subset with the following exclusions:

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

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

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 CIs, to summarize the proportion of subjects reporting each symptom, any injection site symptom and any systemic symptom. Summaries of solicited AEs will be presented separately for each study vaccination as well as overall study vaccinations by

treatment arm. The proportion of subjects reporting symptoms may be compared between treatment arms using Chi-square or Fisher's exact test. The proportion of subjects reporting solicited symptoms between the different study vaccinations (i.e., first and second) will be compared using McNemar's test.

Unsolicited AEs will be coded by Medical Dictionary for Regulatory Activities (MedDRA®) for preferred term and system organ class (SOC). The numbers of SAEs 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 strain-specific 2013 and 2017 A/H7N9 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 <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), 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 or non-study pandemic 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 vaccine dosage and adjuvant use as well as study vaccination schedule on the elicited immune response. For example, logistic regression may be used to examine the relationship of proportion of responders

with study vaccine dosage and adjuvant use as well as study vaccination schedule, and available covariates may be considered for inclusion in the model.

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 2013 and 2017 A/H7N9 responses and association with study vaccine dosage and adjuvant use as well as study vaccination schedule.

In addition, N9 NA-specific antibody assays are in development. N9 NA-specific serum antibody responses may be assessed at baseline as well as immediately prior to and approximately 21 days after the second study vaccination. For each time point, summaries may include number and percentage of subjects with detectable N9 NA response (to be defined in SAP 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 N9 NA-specific serum antibody responses with HAI and Neut antibody titers will be evaluated, and plots such as reverse cumulative distributions or longitudinal presentations of GMTs will be presented.

Furthermore, a determination of the N9 NA content in the 2013 and 2017 A/H7N9 IIVs is planned, and may be used to correlate the NA content of the 2013 and 2017 A/H7N9 IIVs with the elicited N9 NA-specific serum antibody responses. Detectable N9 NA-specific serum 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 content, HA antigen dosage, adjuvant, and study vaccination schedule.

At least a subset of samples will also be tested for exploratory immunogenicity endpoints, including cellular immunology and additional serological assays. Exploratory immunology analyses will be primarily descriptive and defined in the SAP. Results of any exploratory immunogenicity analysis will not be published prior to publication of the primary immunogenicity results for this trial.

Further immunogenicity testing and/or analyses may be carried out in the future based upon subjects' prior receipt of non-seasonal influenza vaccine, 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 clinical trial, in compliance with ICH E6 GCP Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Each participating VTEU site will permit the study monitor or other authorized representatives of DMID as well as governmental regulatory agencies, such as the FDA, 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 this clinical 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 clinical 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 (and its subcontractors) is responsible for conducting routine quality assurance (QA) and quality control (QC) activities to internally monitor study progress and protocol compliance. Each site PI 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 PI will ensure all study personnel are appropriately trained and applicable 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 PIs 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 (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 21 CFR 56, as applicable. The site PIs will also ensure conformity with ICH E6 GCP and applicable federal regulations, guidance and guidelines for GCP and Clinical Trials with humans.

14.2 Institutional Review Board (IRB)

Each institution engaged in this research will hold a current Federalwide Assurance (FWA) issued by the Office for Human Research Protections (OHRP) for federally funded research. The IRB must be registered with OHRP [OHRP-only or OHRP/FDA] as applicable to the research. The IRB FWA number will be provided to DMID.

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

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

14.3 Informed Consent Process

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continuing throughout the individual's trial participation. Before any study procedures

are performed, informed consent will be obtained and documented. Subjects will receive a concise and focused presentation of key information about the trial, verbally and with a written ICF. The explanation will be organized, and presented in lay terminology and language that facilitates understanding why one might or might not want to participate. The ICF must not include any exculpatory statements.

The site PIs or their designees will describe the protocol to potential subjects face-to-face. The key information about the purpose of the trial, the procedures and experimental aspects of the trial, risks and discomforts, any expected benefits to the subject, and alternative treatment will be presented first to the subject.

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

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

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

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

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

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

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

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

New information that significantly impacts the subject's risk of receiving the study interventions/study products will be communicated by the site PIs or their designees to the subjects who consent to participate in the trial in accordance with IRB requirements. The ICF will be updated and subjects will be re-consented in accordance with IRB requirements, if necessary. Subjects will be given a copy of all ICFs that they sign.

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

After all subjects had enrolled, it was determined that B cell repertoire sequencing is a form of genetic testing that will be performed as part of this trial under this primary research protocol. Subjects will be informed and asked for their consent to use their samples/specimens and information for genetic testing, such as B cell repertoire sequencing. B cell repertoire sequencing results (data) may be shared broadly with other researchers but will not be shared with subjects. Individual results will be stored indefinitely in an NIH restricted-access database, and a summary of results may be placed in an unrestricted (open) database.

The samples/specimens will be encoded (labeled) only with a barcode and a unique tracking number to protect subject confidentiality. The genetic data in the NIH database will be coded in

such a way that information will be considered de-identified. Subjects will be informed of the risks, including potential for re-identification and possible harm from the mis-use of data, however, NIH will require researchers to not re-identify the subjects.

Subjects will have the right to withdraw consent for the use of their samples/specimens and/or data without penalty at any time. Samples/specimens and data that have already been used for primary research may not be able to be withdrawn.

"Written", or "signed", refers to the *use of* or *writing on* a paper or an electronic ICF. Re-consent (revised or separate consent form) for primary research using samples/specimens and information for genetic testing, such as B cell repertoire sequencing, may use paper or electronic ICFs to obtain the subject's written consent. The subject will have a discussion with study staff, who is able to answer the subject's questions, including if re-consent is obtained off-site. A paper copy of the signed ICF will be given to the subject in person or mailed.

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

This trial will be inclusive of all subjects, 19 to 50 years of age, 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 [74]. Should the outcome of this trial be deemed acceptable, additional trials may be initiated including those in other populations.

It is unknown if the 2013 and 2017 A/H7N9 IIVs with or without AS03 adjuvant pose any risks to an unborn child. As of November 22, 2015 (per the GSK AS03 Adjuvant Investigator's Brochure dated February 2016), 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 <1 year has passed since the last menses if menopausal must agree to practice highly effective contraception that may include non-male sexual relationships, abstinence from sexual intercourse with a male partner, monogamous relationship with a 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/cervical cap **with** spermicide, effective intrauterine devices, NuvaRing®, and licensed hormonal methods such as implants, injectables or oral contraceptives ("the pill"), with use of a highly effective method of contraception for a minimum of 30 days prior to study

vaccine exposure and agree to practice highly effective contraception for the duration of study vaccine 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 PIs, other study personnel, the sponsor, and their agents. This confidentiality includes documentation, investigation data, subject's clinical information, and all other information generated during participation in this trial. No information concerning this trial or the data generated from this trial will be released to any unauthorized third party without prior written approval of the subject and DMID.

Subject confidentiality will be maintained when trial results are published or discussed in conferences, and is extended to cover testing of samples/specimens. The study monitor or other authorized representatives of DMID as well as governmental regulatory agencies, such as the FDA, may inspect all documents and records required to be maintained by the site PIs. 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.

All records will be kept locked and all computer entry and networking programs will be carried out with coded numbers only and with password-protected systems. All non-clinical samples/specimens, evaluation forms, reports, and other records that leave the site will be identified only by a coded number and will not be identified by the subject's name.

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 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 US Government that is used for auditing or evaluation of federally funded projects, like this trial, or

for information that must be released in order to meet the requirements of the 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 prematurely terminated by the sponsor, any regulatory authority, the site PI, or appropriate sub-investigator for any reason, the site PI or appropriate sub-investigator will promptly inform the subjects and assure appropriate therapy or follow-up for the subjects, as necessary. The site PI or appropriate sub-investigator will provide a detailed written explanation of the termination to the IRB. If any subject's private information will continue to be collected for this trial, the IRB must approve an ICF with the study procedures, any risks and discomforts as well as applicable elements, and the site PI or designee will re-consent the subjects as approved by the IRB.

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 the research tests, study procedures/evaluations or study vaccine while taking part in this trial.

Subjects may be compensated for their participation in this trial. Compensation will be in accordance with local IRB requirements, and subject to local IRB approval.

If it is determined by the participating VTEU site and the site PI that an injury occurred to a subject as a direct result of the tests or treatments that are done for this trial, then referrals to appropriate health care facilities will be provided to the subject. Study personnel will try to reduce, control and treat any complications from this trial. Immediate medical treatment may be provided by the participating 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 NIAID, NIH or the participating VTEU site for any injury suffered due to participation in this trial.

For this protocol, the study products (2013 and 2017 A/H7N9 IIVs manufactured by Sanofi Pasteur and AS03 adjuvant manufactured by GSK) are covered under the PREP Act, as described in Section 2.1.1.

14.8 Future Use of Stored Specimens

Subjects who agree to participate in this trial will have venous blood collected for ESR and clinical safety laboratory evaluations, serological and cellular immunology assays as well as future research.

Residual samples/specimens are those that are left over after protocol-specified testing for serological and cellular immunology assays and this trial have been completed. Any remaining (residual) specimens (serum, plasma and PBMCs) derived from venous blood samples collected for serological and cellular immunology assays will be kept for possible use in future research studies, such as examining additional immunological assessments or testing for antibodies against other viruses or bacteria. Residual specimens for future research use will be stored indefinitely at a central clinical storage facility and may be shared for purposes other than PP analysis with investigators at the participating VTEU site and with other investigators at other institutions once the CSR has been finalized. An IRB will review future research prior to the use of identifiable specimens or data.

Additional venous blood samples for serum, plasma and PBMC specimens will be collected during this trial specifically for the purpose of future research, including, but not limited to, detailed systems biology analyses, antibody epitope mapping, B and T cell repertoire determination, non-traditional immune assay development, assessing innate immune factors, and the ability of A/H7 study vaccine-induced antibodies to cross-react with other influenza viruses. These samples/specimens might be used in new or different immunological laboratory tests, to provide information for the development of new vaccines, or for the studies of influenza or other infections. Samples/specimens collected during this trial specifically for the purpose of future research will be stored indefinitely at a central clinical storage facility and may be shared with investigators at the participating VTEU site and with other investigators at other institutions. An IRB will review future research prior to the use of identifiable specimens or data.

Residual specimens will be available upon the completion of this trial; however, samples/specimens collected during this trial specifically for the purpose of future research may be requested from DMID and shipped from the DMID CMS at any time.

There are no benefits to subjects in the collection, storage and future research use of their samples/specimens. Future research tests may benefit others by leading to new approaches in the development of vaccines or treatments for influenza. Future research use samples/specimens (residual specimens and samples/specimens collected during this trial specifically for the purpose of future research) will not be sold or used directly for production of any commercial product. Each sample/specimen will be encoded (labeled) only with a barcode and a unique tracking number to protect subject confidentiality. Reports from future research studies performed using subjects' samples/specimens will NOT be kept in their health records and results will not be shared with subjects.

Subjects will **not** be given the option to decide if they want their **residual** specimens to be used for future research or have these specimens destroyed at the end of this trial. Subjects will be asked to consent to the future research use of **residual** specimens as a condition of their study participation.

Subjects will **not** be given the option to decide if they want their samples/specimens collected during this trial **specifically for the purpose of future research** to be used for future research or have these samples/specimens destroyed at the end of this trial. These samples/specimens are protocol-required; thus, subjects will be asked to consent to the future research use of these samples/specimens as a condition of their study participation.

By signing a written ICF for this trial, subjects agree to the collection, storage and future research use of their samples/specimens (residual specimens and samples/specimens collected during this trial specifically for the purpose of future research).

After all subjects had enrolled, it was determined that genetic testing may be performed on residual specimens and samples/specimens collected during this trial specifically for the purpose of future use, under a secondary research protocol. Secondary research is research that is not part of this trial and will be performed in the future. Subjects will be informed and asked for their consent to use their residual specimens and samples/specimens collected during this trial specifically for the purpose of future research and information for genetic testing for "secondary research". Genetic testing could include transcriptomics, whole genome or exome sequencing, or other types of genetic testing. This could contribute to identifying genetic factors involved in vaccine responses. Genetic testing results (data) may be shared broadly with other researchers but will not be shared with subjects. Individual results will be stored indefinitely in an NIH restricted-access database, and a summary of results may be placed in an unrestricted (open) database.

The samples/specimens will be labeled as above for storage. The genetic data in the NIH database will be coded in such a way that information will be considered de-identified. Subjects

will be informed of the risks, including potential for re-identification and possible harm from the mis-use of data, however, NIH will require researchers to not re-identify the subjects.

Subjects will have the right to withdraw consent for the use of their samples/specimens and/or data without penalty at any time. Samples/specimens and data that have already been used for secondary research may not be able to be withdrawn.

"Written", or "signed", refers to the *use of* or *writing on* a paper or an electronic ICF. Re-consent (revised or separate consent form) for secondary research using samples/specimens and information, such as for genetic testing, may use paper or electronic ICFs to obtain the subject's written consent. The subject will have a discussion with study staff, who is able to answer the subject's questions, including if re-consent is obtained off-site. A paper copy of the signed ICF will be given to the subject in person or mailed.

15 DATA HANDLING AND RECORD KEEPING

The site PIs are 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 PIs 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 PI 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 PI. During this trial, the site PIs 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, and reactogenicity and immunogenicity data).

15.4 Timing/Reports

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

Analysis of exploratory immunogenicity endpoints, including cellular immunology and additional serological assays, 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.

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 assignment. In this regard, the participating VTEU sites requesting such information to share with subjects must do so in accordance with IRB requirements.

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. These documents will be retained for a longer period, however, if required by local regulations. ICFs for future research use will be maintained as long as the sample/specimen exists.

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

15.6 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 PI or other study personnel. As a result of protocol deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6 GCP guidelines:

4.5 Compliance with Protocol, Sections 4.5.1, 4.5.2 and 4.5.3

5.1 Quality Assurance and Quality Control, Section 5.1.1

5.20 Noncompliance, Sections 5.20.1 and 5.20.2

It is the responsibility of the site PI and other study personnel to use continuous vigilance to identify and report protocol deviations within five working days of identification of the protocol deviation, or within five working days of the scheduled protocol-required activity. Protocol deviations must be promptly reported to DMID, via the SDCC's AdvantageEDC^{SM}.

Protocol deviations, as defined above, must be addressed on the appropriate DCF. A completed copy of the Protocol Deviation DCF must be maintained in the regulatory file as well as in the

subject's chart. Protocol deviations must be sent to the IRB in accordance with IRB requirements. The site PI and other study personnel are responsible for knowing and adhering to IRB requirements.

16 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 all 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 clinical trial, the responsible party is DMID which will register this 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

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Appendices

APPENDIX A. SCHEDULE OF STUDY PROCEDURES AND EVALUATIONS

Table 15: Vaccination Period for Treatment Arms 1 and 4

Study Visit Number	**V00**	**V01**	**V02**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08**	**V09**	**V10**	**V11**
Study Day post first study vaccination	**Screening (Optional) D-28 to -1**	**Enrollment Dose 1 D1**	**D2+1d**	**D4+1d**	**D8-1/+2d**	**D15±1d**	**D22+7d**	***D23***	***D25***	***D29***	***D36***	***D43***
Study Day post second study vaccination							**Dose 2 D1**	**D2+1d**	**D4+1d**	**D8-1/+2d**	**D15±1d**	**D22+7d**
Study Procedure/Evaluation												
Informed Consent$^{\infty}$	X	X$^{\dagger\neg}$										
Demographic Information	X	X$^{\dagger *}$										
Eligibility Criteria	X	X$^{\dagger\neg 1}$					X$^{\dagger 1}$					
Medical History$^{@}$	X	X$^{\dagger\neg}$	X	X	X	X	X†	X	X	X	X	X
Concomitant Medications§	X	X$^{\dagger\neg}$	X	X	X	X	X†	X	X	X	X	X
Vital Signs (Oral Temperature$^{\%}$, Pulse and BP)	X	X$^{\dagger\$}$					X$^{\dagger 2}$					
Height and Weight	X	X$^{\dagger *}$										
Physical Examination	X^{3}	X$^{\dagger 3 * \{\}}$	{X}	{X}	{X}	{X}	{X}†	{X}	{X}	{X}	{X}	{X}
Urine or Serum Pregnancy Test	X$^{\wedge}$	X$^{\dagger\wedge}$					X$^{\dagger\wedge}$					
Venous Blood Collection for ESR	X$^{\neq}$	X$^{\neq *}$										
Enrollment in AdvantageEDC^{SM} and Randomization		X†										
Venous Blood Collection for Clinical Safety Laboratory Evaluations~		X$^{\dagger\#}$			X		X†			X		
Venous Blood Collection for Serological Assays		X†					X$^{\dagger\Psi}$					X
Venous Blood Collection for Cellular Immunology Assays		X†	X	X	X	X	X†	X	X	X	X	
Venous Blood Collection for Future Research		X†	X	X	X	X	X†	X	X	X	X	X
Pre-Administration Reactogenicity Assessments		X†					X†					
Study Vaccination		X					X					

Study Visit Number	**V00**	**V01**	**V02**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08**	**V09**	**V10**	**V11**
Study Day post first study vaccination	**Screening (Optional) D-28 to -1**	**Enrollment Dose 1 D1**	**D2+1d**	**D4+1d**	**D8-1/+2d**	**D15±1d**	**D22+7d**	***D23***	***D25***	***D29***	***D36***	***D43***
Study Day post second study vaccination							**Dose 2 D1**	**D2+1d**	**D4+1d**	**D8-1/+2d**	**D15±1d**	**D22+7d**
Study Procedure/Evaluation												
20-minute Evaluation After Study Vaccination		X					X					
Examine Study Vaccination Site		X	X	X	X		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	X	X		
AE/SAE Assessment		X[&]	X[&]	X[&]	X[&]	X	X[&4]	X[&4]	X[&4]	X[&4]	X[4]	X[4]

∞ Prior to study procedures.

¬ Review/confirm information or activity in subjects previously consented and screened.

† Prior to study vaccination.

* Not required if done at the optional screening visit.

1 Review results of ESR or clinical safety laboratory 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, and interim medical history will be obtained by interview of subjects at follow-up visits after the first study vaccination.

ς Receipt of any 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.

2 Vital signs are not required for subjects who are discontinued from receipt of the second study vaccination and being followed for safety.

3 At the screening visit (optional) or on Day 1 prior to the first study vaccination, 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, and as an assessment for signs suggestive of PIMMCs.

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

^ Performed locally by the site at the screening visit (optional) or within 24 hours prior to each study vaccination for all women of childbearing potential. Results must be negative and known prior to randomization on Day 1 and administration of each study vaccination.

≠ Performed locally by the site at the screening visit (optional) or on Day 1 prior to the first study vaccination. The ESR value must be confirmed as less than 30 mm per hour prior to randomization on Day 1 and administration of the first study vaccination.

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

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

Ψ Subjects who receive only one dose of study vaccine will be encouraged to remain in this trial for follow-up safety assessments (may be conducted by phone call rather than in person) continuing through approximately 12 months after their last study vaccination. These subjects will also be encouraged to provide a venous blood sample for serological assays approximately 21 and 180 days after their last study vaccination.

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

4 AEs limited to SAEs and MAAEs, including NOCMCs and PIMMCs, for subjects who are discontinued from receipt of the second study vaccination and being followed for safety.

Table 16: Follow-Up Period for Treatment Arms 1 and 4 (Including Early Termination and Unscheduled Visits)

Study Visit Number	**V12****	**V13**	**V14****	**V15**	**V16****	**Early Termination (if needed)**	**Unscheduled (if needed)**
Study Day post first study vaccination	***D82***	***D112***	***D142***	***D202***	***D387***		
Study Day post second study vaccination	**D61±7d**	**D91±14d**	**D121±14d**	**D181±14d**	**D366±14d**		
Study Procedure/Evaluation							
Medical History[@]		X		X		X	X (if indicated)
Concomitant Medications[ς]	X	X	X	X		X (if prior to 21 days after last study vaccination and receipt of any non-study influenza vaccines if within 180 days after last study vaccination)	X (if prior to 21 days after last study vaccination and receipt of any non-study influenza vaccines if within 180 days after last study vaccination)
Vital Signs (Oral Temperature[%], Pulse and BP)						X (may be obtained if indicated)	X (may be obtained if indicated)
Physical Examination		{X}		{X}		{X}	{X}
Venous Blood Collection for Clinical Safety Laboratory Evaluations~						X (if within 7 days after last study vaccination)	X (if indicated)
Venous Blood Collection for Serological Assays				X[Ψ]		X (if within 21 days after last study vaccination)	X (if within 21 days after last study vaccination)
Venous Blood Collection for Cellular Immunology Assays		X		X		X (if within 21 days after last study vaccination)	X (if within 21 days after last study vaccination)
Venous Blood Collection for Future Research		X		X		X (if within 21 days after last study vaccination)	X (if within 21 days after last study vaccination)
Examine Study Vaccination Site						X (if within 7 days after last study vaccination)	X (if within 7 days after last study vaccination)

Study Visit Number	**V12****	**V13**	**V14****	**V15**	**V16****	**Early Termination (if needed)**	**Unscheduled (if needed)**
Study Day post first study vaccination	***D82***	***D112***	***D142***	***D202***	***D387***		
Study Day post second study vaccination	**D61±7d**	**D91±14d**	**D121±14d**	**D181±14d**	**D366±14d**		
Study Procedure/Evaluation							
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 (if after 21 days after last study vaccination)	X (if after 21 days after last study vaccination)

**Phone call assessment.

@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, and interim medical history will be obtained by interview of subjects at follow-up visits after the first study vaccination.

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

% 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 receive only one dose of study vaccine will be encouraged to remain in this trial for follow-up safety assessments (may be conducted by phone call rather than in person) continuing through approximately 12 months after their last study vaccination. These subjects will also be encouraged to provide a venous blood sample for serological assays approximately 21 and 180 days after their last study vaccination.

! AEs limited to SAEs and MAAEs, including NOCMCs and PIMMCs, that have occurred since the previous clinic visit or phone call.

Table 17: Vaccination Period for Treatment Arms 2, 3, 5, and 6

Study Visit Number	**V00**	**V01**	**V02**	**V03**	**V04**	**V05**	**V06**	**V07****	**V08**	**V09**	**V10**	**V11**	**V12**	**V13**
Study Day post first study vaccination	**Screening (Optional) D-28 to -1**	**Enrollment Dose 1 D1**	**D2+1d**	**D4+1d**	**D8-1/+2d**	**D15±1d**	**D22+7d**	**D61±7d**	**D121-7/+14d**	***D122***	***D124***	***D128***	***D135***	***D142***
Study Day post second study vaccination									**Dose 2 D1**	**D2+1d**	**D4+1d**	**D8-1/+2d**	**D15±1d**	**D22+7d**
Study Procedure/Evaluation														
Informed Consent∞	X	X†¬												
Demographic Information	X	X†*												
Eligibility Criteria	X	X†¬[1]							X†[1]					
Medical History@	X	X†¬	X	X	X	X	X	Xς	X†	X	X	X	X	X
Concomitant Medicationsς	X	X†¬	X	X	X	X	X	X	X†	X	X	X	X	X
$Vital Signs (Oral Temperature%, Pulse and BP)	X	X†$							X†[2]					
Height and Weight	X	X†*												
Physical Examination	X[3]	X†[3]*{}	{X}	{X}	{X}	{X}	{X}		{X}†	{X}	{X}	{X}	{X}	{X}
Urine or Serum Pregnancy Test	X^	X†^							X†^					
Venous Blood Collection for ESR	X≠	X≠*												
Enrollment in AdvantageEDC℠ and Randomization		X†												
Venous Blood Collection for Clinical Safety Laboratory Evaluations~		X†#			X				X†			X		
Venous Blood Collection for Serological Assays		X†					X		X†Ψ					X
Venous Blood Collection for Cellular Immunology Assays		X†	X	X	X	X			X†	X	X	X	X	
Venous Blood Collection for Future Research		X†	X	X	X	X	X		X†	X	X	X	X	X
Pre-Administration Reactogenicity Assessments		X†							X†					
Study Vaccination		X							X					

Study Visit Number	**V00**	**V01**	**V02**	**V03**	**V04**	**V05**	**V06**	**V07****	**V08**	**V09**	**V10**	**V11**	**V12**	**V13**
Study Day post first study vaccination	**Screening (Optional) D-28 to -1**	**Enrollment Dose 1 D1**	**D2+1d**	**D4+1d**	**D8-1/+2d**	**D15±1d**	**D22+7d**	**D61±7d**	**D121-7/+14d**	***D122***	***D124***	***D128***	***D135***	***D142***
Study Day post second study vaccination									**Dose 2 D1**	**D2+1d**	**D4+1d**	**D8-1/+2d**	**D15±1d**	**D22+7d**
Study Procedure/Evaluation														
20-minute Evaluation After Study Vaccination		X							X					
Examine Study Vaccination Site		X	X	X	X				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	X	X		
AE/SAE Assessment		X[&]	X[&]	X[&]	X[&]	X	X	X[!]	X[&]	X[&4]	X[&4]	X[&4]	X[4]	X[4]

**Phone call assessment.

∞ Prior to study procedures.

¬ Review/confirm information or activity in subjects previously consented and screened.

† Prior to study vaccination.

* Not required if done at the optional screening visit.

1 Review results of ESR or clinical safety laboratory 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, and interim medical history will be obtained by interview of subjects at follow-up visits after the first study vaccination.

ς Receipt of any 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.

2 Vital signs are not required for subjects who are discontinued from receipt of the second study vaccination and being followed for safety.

3 At the screening visit (optional) or on Day 1 prior to the first study vaccination, 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, and as an assessment for signs suggestive of PIMMCs.

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

^ Performed locally by the site at the screening visit (optional) or within 24 hours prior to each study vaccination for all women of childbearing potential. Results must be negative and known prior to randomization on Day 1 and administration of each study vaccination.

≠ Performed locally by the site at the screening visit (optional) or on Day 1 prior to the first study vaccination. The ESR value must be confirmed as less than 30 mm per hour prior to randomization on Day 1 and administration of the first study vaccination.

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

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

Ψ Subjects who receive only one dose of study vaccine will be encouraged to remain in this trial for follow-up safety assessments (may be conducted by phone call rather than in person) continuing through approximately 12 months after their last study vaccination. These subjects will also be encouraged to provide a venous blood sample for serological assays approximately 21 and 180 days after their last study vaccination.

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

! AEs limited to SAEs and MAAEs, including NOCMCs and PIMMCs, that have occurred since the previous clinic visit or phone call.

4 AEs limited to SAEs and MAAEs, including NOCMCs and PIMMCs, for subjects who are discontinued from receipt of the second study vaccination and being followed for safety.

Table 18: Follow-Up Period for Treatment Arms 2, 3, 5, and 6 (Including Early Termination and Unscheduled Visits)

Study Visit Number	**V14**[**]	**V15**	**V16**[**]	**V17**	**V18**[**]	**Early Termination (if needed)**	**Unscheduled (if needed)**
Study Day post first study vaccination	***D181***	***D211***	***D241***	***D301***	***D486***		
Study Day post second study vaccination	**D61±7d**	**D91±14d**	**D121±14d**	**D181±14d**	**D366±14d**		
Study Procedure/Evaluation							
Medical History[@]		X		X		X	X (if indicated)
Concomitant Medications[ς]	X	X	X	X		X (if prior to 21 days after last study vaccination and receipt of any non-study influenza vaccines if within 180 days after last study vaccination)	X (if prior to 21 days after last study vaccination and receipt of any non-study influenza vaccines if within 180 days after last study vaccination)
Vital Signs (Oral Temperature[%], Pulse and BP)						X (may be obtained if indicated)	X (may be obtained if indicated)
Physical Examination		{X}		{X}		{X}	{X}
Venous Blood Collection for Clinical Safety Laboratory Evaluations~						X (if within 7 days after last study vaccination)	X (if indicated)
Venous Blood Collection for Serological Assays				X[Ψ]		X (if within 21 days after last study vaccination)	X (if within 21 days after last study vaccination)
Venous Blood Collection for Cellular Immunology Assays		X		X		X (if within 21 days after last study vaccination)	X (if within 21 days after last study vaccination)
Venous Blood Collection for Future Research		X		X		X (if within 21 days after last study vaccination)	X (if within 21 days after last study vaccination)
Examine Study Vaccination Site						X (if within 7 days after last study vaccination)	X (if within 7 days after last study vaccination)

Study Visit Number	**V14****	**V15**	**V16****	**V17**	**V18****	**Early Termination (if needed)**	**Unscheduled (if needed)**
Study Day post first study vaccination	***D181***	***D211***	***D241***	***D301***	***D486***		
Study Day post second study vaccination	**D61±7d**	**D91±14d**	**D121±14d**	**D181±14d**	**D366±14d**		
Study Procedure/Evaluation							
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 (if after 21 days after last study vaccination)	X (if after 21 days after last study vaccination)

**Phone call assessment.

@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, and interim medical history will be obtained by interview of subjects at follow-up visits after the first study vaccination.

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

% 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 receive only one dose of study vaccine will be encouraged to remain in this trial for follow-up safety assessments (may be conducted by phone call rather than in person) continuing through approximately 12 months after their last study vaccination. These subjects will also be encouraged to provide a venous blood sample for serological assays approximately 21 and 180 days after their last study vaccination.

! AEs limited to SAEs and MAAEs, including NOCMCs and PIMMCs, that have occurred since the previous clinic visit or phone call.

APPENDIX B. SCHEDULE OF SPECIAL ASSAYS

Table 19: Special Assays for All Treatment Arms

Assay	Days Relative to Priming (First) Dose													
	D1	D2	D4	D8	D15	D22								
	Days Relative to Boosting (Second) Dose													
							D1	D2	D4	D8	D15	D22	D91	D181
Serological Assays														
HAI, Neut, HA Stem, NA, NAI	X					X	X					X		X
Cellular Immunology Assays														
MBCs by Enzyme-Linked Immunosorbent Spot (ELISpot) or Fluorescence-Activated Cell Sorting (FACS)	X												X	X
Plasmablasts (ASCs)by ELISpot[@]				X						X				
CD4 and CD8 T Cells Multifunctional Analyses by Intracellular Staining (ICS)	X			X			X			X			X	
Phenotyping: cT_{FH} Cells by FACS	X		X	X	X		X		X	X	X			
Innate Immune Cells/B Cell Activation by FACS	X	X	X	X	X		X	X	X	X	X			
B Cell Receptor Somatic Hypermutation and Repertoire Assessments	X													X
Future Research														
Future Research	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[@] All sites will collect venous blood for this assay. Specified sites will utilize freshly isolated PBMCs. All other sites will process for frozen PBMCs.

Table 20: Clinical Laboratory Evaluations, Special Assays and Venipuncture Volumes for Treatment Arms 1 and 4

Study Visit Number	V00	V01	V02	V03	V04	V05	V06	V07	V08	V09	V10	V11	V13	V15	Cumulative BV Total (mL)
Study Procedure/Evaluation	Days Relative to Priming (First) Dose														
	Scrn	D1	D2	D4	D8	D15	D22	D23	D25	D29	D36	D43	D112	D202	
	Days Relative to Boosting (Second) Dose														
							D1	D2	D4	D8	D15	D22	D91	D181	
Study Vaccination		X					X								
Clinical Laboratory Evaluations															
ESR	4^	–^*													**4**
Clinical Safety Laboratory Evaluations~		10#†			10		10†			10					**40**
Serological Assays															
HAI, Neut, HA Stem, NA, NAI		15†					15†					15		15	**60**
Cellular Immunology Assays (CIA)															
MBCs by Enzyme-Linked Immunosorbent Spot (ELISpot) or Fluorescence-Activated Cell Sorting (FACS)		16†											16	16	**48**
Plasmablasts (ASCs) by ELISpot@					12					12					**24**
CD4 and CD8 T Cells Multifunctional Analyses by Intracellular Staining (ICS)		24†			24		24†			24			24		**120**
Phenotyping: cT_{FH} Cells by FACS		4†		4	4	4	4†		4	4	4				**32**
Innate Immune Cells/B Cell Activation by FACS		4†	4	4	4	4	4†	4	4	4	4				**40**
B Cell Receptor Somatic Hypermutation and Repertoire Assessments		16†												16	**32**
Future Research (FR)															
Future Research		16†	16	16	21	16	16†	16	16	21	16	16	16	16	**218**

Breakdown of Future Research Samples															
'Omics (Plasma/PBMCs) – specified sites only		12	12	12	12		12	12	12	12					**96**
Serum – all sites					5					5					**10**
Plasma/PBMCs		4[1] or 16[2]	4[1] or 16[2]	4[1] or 16[2]	4[1] or 16[2]	16[3]	4[1] or 16[2]	4[1] or 16[2]	4[1] or 16[2]	4[1] or 16[2]	16[3]	16[3]	16[3]	16[3]	**112[1] or 208[2]**
Per Visit Blood Volume (BV) Totals															
Per Visit CIA/FR Blood Volume Total (mL)		**80**	**20**	**24**	**65**	**24**	**48**	**20**	**24**	**65**	**24**	**16**	**56**	**48**	**514**
Per Visit Blood Volume Total (mL)	**4**	**105**	**20**	**24**	**75**	**24**	**73**	**20**	**24**	**75**	**24**	**31**	**56**	**63**	**618**
Running Blood Volume Totals															
Running Blood Volume Total (mL)	**4**	**109**	**129**	**153**	**228**	**247**	**320**	**340**	**364**	**444**	**458**	**489**	**545**	**618**	

^ Drawn up to 28 days prior to the first study vaccination. The ESR value must be confirmed as less than 30 mm per hour prior to randomization and first study vaccination.

* Not required if done at the optional screening visit.

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

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

† Blood must be drawn immediately prior to study vaccination.

@ All sites will collect venous blood for this assay. Specified sites will utilize freshly isolated PBMCs. All other sites will process for frozen PBMCs.

1 Specified sites only.

2 Sites processing only for Plasma/PBMCs.

3 All sites.

Table 21: Clinical Laboratory Evaluations, Special Assays and Venipuncture Volumes for Treatment Arms 2, 3, 5, and 6

Study Visit Number	V00	V01	V02	V03	V04	V05	V06	V08	V09	V10	V11	V12	V13	V15	V17	Cumulative BV Total (mL)
Study Procedure/Evaluation	Days Relative to Priming (First) Dose															
	Scrn	D1	D2	D4	D8	D15	D22	D121	D122	D124	D128	D135	D142	D211	D301	
	Days Relative to Boosting (Second) Dose															
								D1	D2	D4	D8	D15	D22	D91	D181	
Study Vaccination		X						X								
Clinical Laboratory Evaluations																
ESR	4^	–^*														**4**
Clinical Safety Laboratory Evaluations~		10#†			10			10†			10					**40**
Serological Assays																
HAI, Neut, HA Stem, NA, NAI		15†					15	15†					15		15	**75**
Cellular Immunology Assays (CIA)																
MBCs by Enzyme-Linked Immunosorbent Spot (ELISpot) or Fluorescence-Activated Cell Sorting (FACS)		16†												16	16	**48**
Plasmablasts (ASCs) by ELISpot@					12						12					**24**
CD4 and CD8 T Cells Multifunctional Analyses by Intracellular Staining (ICS)		24†			24			24†			24			24		**120**
Phenotyping: cT_{FH} Cells by FACS		4†		4	4	4		4†		4	4	4				**32**
Innate Immune Cells/B Cell Activation by FACS		4†	4	4	4	4		4†	4	4	4	4				**40**

B Cell Receptor Somatic Hypermutation and Repertoire Assessments		16†													16	**32**
Future Research (FR)																
Future Research		16†	16	16	21	16	16	16†	16	16	21	16	16	16	16	**234**
Breakdown of Future Research Samples																
'Omics (Plasma/PBMCs) – specified sites only		12	12	12	12			12	12	12	12					**96**
Serum – all sites					5						5					**10**
Plasma/PBMCs		4[1] or 16[2]	4[1] or 16[2]	4[1] or 16[2]	4[1] or 16[2]	16[3]	16[3]	4[1] or 16[2]	4[1] or 16[2]	4[1] or 16[2]	4[1] or 16[2]	16[3]	16[3]	16[3]	16[3]	**128[1] or 224[2]**
Per Visit Blood Volume (BV) Totals																
Per Visit CIA/FR Blood Volume Total (mL)		**80**	**20**	**24**	**65**	**24**	**16**	**48**	**20**	**24**	**65**	**24**	**16**	**56**	**48**	**530**
Per Visit Blood Volume Total (mL)	**4**	**105**	**20**	**24**	**75**	**24**	**31**	**73**	**20**	**24**	**75**	**24**	**31**	**56**	**63**	**649**
Running Blood Volume Totals																
Running Blood Volume Total (mL)	**4**	**109**	**129**	**153**	**228**	**247**	**278**	**351**	**371**	**395**	**475**	**489**	**520**	**576**	**649**	

^ Drawn up to 28 days prior to the first study vaccination. The ESR value must be confirmed as less than 30 mm per hour prior to randomization and first study vaccination.

* Not required if done at the optional screening visit.

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

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

† Blood must be drawn immediately prior to study vaccination.

@ All sites will collect venous blood for this assay. Specified sites will utilize freshly isolated PBMCs. All other sites will process for frozen PBMCs.

1 Specified sites only.

2 Sites processing only for Plasma/PBMCs.

3 All sites.

APPENDIX C. 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