A Phase I Study to Assess the Safety, Reactogenicity and Immunogenicity of Two Quadrivalent Seasonal Influenza Vaccines (Fluzone® or Flublok®) With or Without One of Two Adjuvants (AF03 or Advax-CpG55.2) in Healthy Adults 18-45 Years of Age

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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 Pharmaceuticals for Human Use (ICH): Good Clinical Practice (GCP) E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) Guidance for Industry," published in the Federal Register (83 Federal Register 8882 (2018)
- 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
Advax	Trade name for delta inulin adjuvant formulation
AE	Adverse Event/Adverse Experience
AESIs	Adverse Events of Special Interest
AF03	Adjuvant formulation (03)
ALP	Alkaline phosphatase
ALT	Alanine Aminotransferase
ANCA	Anti-Neutrophil Cytoplasmic Antibody
AS03	Adjuvant System (03)
AST	Aspartate Aminotransferase
BARDA	Biomedical Advanced Research and Development Authority
BLA	Biologics License Applications
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
CpG55.2	Class B CpG oligonucleotide adjuvant
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
ELISpot	Enzyme-Linked Immunosorbent Spot
ESR	Erythrocyte Sedimentation Rate
FACS	Fluorescence-Activated Cell Sorting
FDA	Food and Drug Administration
FWA	Federal-wide Assurance
g/dL	Grams per Deciliter
GBS	Guillain-Barré Syndrome
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
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
HLGT	High Level Group Term
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
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
IRB	Institutional Review Board
ISM	Independent Safety Monitor
IU/L	International Unit(s) per Liter
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, DHHS
NIH	National Institutes of Health
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
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
PRN	As Needed
QIV	Quadrivalent Influenza Vaccine

QA	Quality Assurance
QC	Quality Control
RIV	Recombinant Influenza Vaccine
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
SWI	Sterile Water for Injection
TBD	To Be Determined
TIV	Trivalent Influenza Vaccine
TLR	Toll-like Receptor
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 I Study to Assess the Safety, Reactogenicity and Immunogenicity of Two Quadrivalent Seasonal Influenza Vaccines (Fluzone® or Flublok®) With or Without One of Two Adjuvants (AF03 or Advax-CpG55.2) in Healthy Adults 18-45 Years of Age
Phase:	I
Population:	Up to 240 males and non-pregnant females, 18 to 45 years of age, inclusive, who are in good health and meet all eligibility criteria
Number of Sites:	8 Vaccine and Treatment Evaluation Unit (VTEU) sites
Study Duration:	Approximately 18 months
Subject Participation Duration:	Approximately 12 months
Estimated Time to Complete Enrollment:	Approximately 9 weeks

Description of Agents:	• Flublok Quadrivalent Influenza Vaccine (QIV) 2018/2019 Formula manufactured by Sanofi Pasteur (SP).
	• Fluzone Quadrivalent Influenza Vaccine (QIV) 2018/2019 Formula manufactured by SP.
	• Flublok Quadrivalent Influenza Vaccine (QIV) 2019/2020 Formula manufactured by SP.
	• Fluzone Quadrivalent Influenza Vaccine (QIV) 2019/2020 Formula manufactured by SP.
	• AF03 adjuvant manufactured by SP.
	• Advax-CpG55.2 adjuvant is a combination adjuvant comprised of Advax and CpG55.2 adjuvants:
	  o Advax (delta inulin) adjuvant manufactured for Vaxine by Sypharma Pty Ltd.
	  o CpG55.2 oligonucleotide adjuvant manufactured for Vaxine by Nikko Denka Avecia and Sypharma Pty Ltd.

Table 1: Study Objectives and Outcome Measures

Primary Safety Objectives	**Primary Safety Outcome Measures**
• To assess the safety and reactogenicity of 2018/2019 Fluzone and Flublok with and without AF03 or Advax-CpG55.2 adjuvant.	• Occurrence of solicited injection site and systemic reactogenicity events through approximately Day 8 after the first study vaccination. • Occurrence of unsolicited adverse events from the time of the first study vaccination through approximately Day 29. • Occurrence of all SAEs through approximately 12 months following receipt of the first study vaccination. • Occurrence of abnormal clinical safety laboratory AEs from the time of study vaccination through approximately Day 8 after the first study vaccination.
Primary Immunogenicity Objectives	**Primary Immunogenicity Outcome Measures**
• To assess the serum hemagglutination inhibition (HAI) antibody responses against 2018/2019 QIV strains from baseline (Day 1) to approximately Day 29 after receipt of 2018/2019 Fluzone and Flublok with and without AF03 or Advax-CpG55.2 adjuvant.	• The percentage of subjects achieving HAI titer seroconversion against the 2018/2019 QIV strains (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) on approximately Day 29 for each study group. • The percentage of subjects with an HAI titer ≥1:40 against the 2018/2019 QIV strains at baseline and approximately Day 29 for each study group. • Geometric mean titers (GMTs) of serum HAI against the 2018/2019 QIV strains at baseline and approximately Day 29 for each study group.

	• Ratio of GMTs of serum HAI against the 2018/2019 QIV strains between adjuvanted and unadjuvanted study groups at baseline and approximately Day 29. • Geometric mean fold rise (GMFR) in HAI titers from baseline (Day 1) against the 2018/2019 QIV strains at approximately Day 29 for each study group
• To assess the serum neuraminidase inhibition antibody (NAI) responses by enzyme-linked lectin assay (ELLA) against NA antigens in the 2018/2019 QIV from baseline (Day 1) to approximately Day 29 after receipt of 2018/2019 Fluzone and Flublok with and without AF03 or Advax-CpG55.2 adjuvant.	• The percentage of subjects achieving NAI seroconversion (defined as ≥4-fold rise in post vaccination antibody titers against the NA antigens in the 2018/2019 QIV) on approximately Day 29 for each study group. • The serum NAI GMT at baseline (Day 1) and approximately Day 29 for each study group. • Ratio of serum NAI GMT between adjuvanted and unadjuvanted study groups at baseline (Day 1) and approximately Day 29. • Geometric mean fold rise (GMFR) in NAI titers from baseline (Day 1) against NA antigens in the 2018/2019 QIV strains at approximately Day 29 for each study group
• To assess the influenza neutralizing (Neut) antibody titer responses against 2018/2019 QIV strains from baseline (Day 1) to approximately Day 29 after receipt of 2018/2019 Fluzone and Flublok with and without AF03 or Advax- CpG55.2 adjuvant.	• The percentage of subjects achieving Neut titer seroconversion against the 2018/2019 QIV strains (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) on approximately Day 29 for each study group.

	• The percentage of subjects with a Neut titer ≥1:40 against the 2018/2019 QIV strains at baseline (Day 1) and approximately Day 29 for each study group. • Serum Neut GMT at baseline (Day 1) and approximately Day 29 for each study group • Ratio of serum Neut GMT between adjuvanted and unadjuvanted study groups at baseline (Day 1) and approximately Day 29. • Geometric mean fold rise (GMFR) in Neut titers from baseline (Day 1) against the 2018/2019 QIV strains at approximately Day 29 for each study group
Secondary Safety Objectives	**Secondary Safety Outcome Measures**
• To assess protocol specified AESIs, medically-attended adverse events (MAAEs), including new-onset chronic medical conditions (NOCMCs) and potentially immune-mediated medical conditions (PIMMCs) that occur after receipt of study product.	• Occurrence of all protocol specified AESIs, MAAEs, including NOCMCs and PIMMCs, from the time of the first study vaccination through approximately 12 months following the first vaccination.
Secondary Immunogenicity Objectives	**Secondary Immunogenicity Outcome Measures**
• To assess the HAI, Neut and NAI ELLA responses to the 2019/2020 QIV strains prior to (Day 1) and approximately 28 days after vaccination with the 2019/2020 QIV in all study groups	• The percentage of subjects achieving an HAI titer ≥1:40 against 2019/2020 QIV strains approximately on Days D90 (baseline) and D118 (28 days post-2019/2020 vaccine) for each study group. • The percentages of subjects achieving HAI, Neut and NAI titer seroconversion, against 2019/2020 QIV strains on

	approximately Day 118 for each study group (NAI titers will only be assessed on study groups 1,2 and 3). • Serum Neut, HAI and NAI GMTs against 2019/2020 QIV strains approximately on Days D90 (baseline) and D118 (28 days post-2019/2020 QIV) for each study group (NAI titers will only be assessed on study groups 1,2 and 3). • Ratio of serum Neut, HAI and NAI GMTs against 2019/2020 QIV strains between adjuvanted and unadjuvanted study groups approximately on Days D90 (baseline) and D118 (28 days post-2019/2020 QIV). NAI titers will only be assessed on study groups 1,2 and 3. • Serum Neut, HAI and NAI GMFRs against 2019/2020 QIV strains from baseline (D90) on approximately D118 for each study group (NAI titers will only be assessed on study groups 1,2 and 3).
• To assess the HAI antibody responses against heterologous influenza A/H1 and H3 strains from baseline (Day 1) to approximately Days 8, 29, 57, 90, and 118 after receipt of 2018/2019 Fluzone or Flublok with and without AF03 or Advax-CpG55.2 adjuvant.	• The percentages of subjects achieving HAI titer seroconversion, against heterologous H1 and H3 influenza strains on approximately Days 8, 29, 57, 90, and 118 for each study group. • The percentage of subjects achieving an HAI titer ≥1:40 against heterologous H1 and H3 influenza strains at baseline (Day 1) and approximately Days 8, 29, 57, 90, and 118 for each study group. • Serum HAI GMT against heterologous H1 and H3 influenza strains at baseline (Day 1) and approximately Days 8, 29, 57, 90, and 118 for each study group. • Ratio of serum HAI GMT against heterologous H1 and H3 influenza strains

	between adjuvanted and unadjuvanted study groups at baseline (Day 1) and approximately Days 8, 29, 57, 90, and 118. • Geometric mean fold rise (GMFR) in HAI from baseline (Day 1) against heterologous H1 and H3 influenza strains at approximately Days 8, 29, 57, 90, and 118 for each study group
• To assess NAI ELLA responses against heterologous N1 and N2 NA antigens from baseline (Day 1) to approximately Days 8, 29, 57, 90, and 118 after administration of 2018/2019 Fluzone with and without AF03 or Advax-CpG55.2 adjuvant.	• The percentage of subjects achieving seroconversion against heterologous N1 and N2 NA antigens on approximately Days 8, 29, 57, 90, and 118 for study groups 1, 2 and 3. • Serum NAI GMTs against heterologous N1 and N2 NA antigens at baseline and approximately Days 8, 29, 57, 90, and 118 for study groups 1, 2 and 3. • Ratio of serum NAI GMTs against heterologous N1 and N2 NA antigens between adjuvanted and unadjuvanted study groups at baseline and approximately Days 8, 29, 57, 90, and 118 (NAI titers will only be assessed on study groups 1,2 and 3). • Geometric mean fold rise (GMFR) in serum NAI from baseline against heterologous N1 and N2 NA antigens at baseline and approximately Days 8, 29, 57, 90, and 118 for study groups 1, 2 and 3.
• To assess the influenza neutralizing (Neut) antibody titer responses against heterologous influenza A/H1 and H3 strains from baseline (Day 1) to approximately Days 8,	• The percentage of subjects achieving Neut titer seroconversion against heterologous H1 and H3 influenza strains

29, 57, 90, and 118 after administration of 2018/2019 Fluzone and Flublok with and without AF03 or Advax-CpG55.2 adjuvant.	on approximately Days 8, 29, 57, 90, and 118 for each study group. • Serum Neut GMT against heterologous H1 and H3 influenza strains at baseline (Day 1) and approximately Days 8, 29, 57, 90, and 118 for each study group. • Ratio of serum Neut GMT against heterologous H1 and H3 influenza strains between adjuvanted and unadjuvanted study groups at baseline (Day 1) and approximately Days 8, 29, 57, 90, and 118. • Geometric mean fold rise (GMFR) of neut antibody titers from baseline against heterologous H1 and H3 influenza strains at baseline (Day 1) and approximately Days 8, 29, 57, 90, and 118 for each study group.
• To assess the longitudinal kinetics and durability of the HAI, NAI, and Neut responses against the 2018/2019 QIV strains on approximately Days 8, 57, 90, and 118 following receipt of the 2018/2019 Fluzone and Flublok with and without AF03 or Advax-CpG55.2 adjuvant.	• The percentage of subjects achieving HAI, NAI and Neut titer seroconversion against 2018/2019 QIV antigens and strains on approximately Days 8, 57, 90, and 118 for each study group (NAI titers will only be assessed on study groups 1,2 and 3). • The percentage of subjects achieving an HAI and Neut titer ≥1:40 against 2018/2019 QIV strains on approximately Days 8, 57, 90, and 118 for each study group (NAI titers will only be assessed on study groups 1,2 and 3). • Serum Neut, HAI and NAI GMT against 2018/2019 QIV strains on approximately Days 8, 57, 90, and 118 for each study group (NAI titers will only be assessed on study groups 1,2 and 3).

	• Ratio of serum Neut, HAI and NAI GMT against 2018/2019 QIV strains between adjuvanted and unadjuvanted study groups on approximately Days 8, 57, 90, and 118 (NAI titers will only be assessed on study groups 1,2 and 3). • Geometric mean fold rise (GMFR) in HAI, Neut and NAI titers from baseline (Day 1) against the 2018/2019 QIV strains at approximately Day 8, 57, 90, and 118 for each study group (NAI titers will only be assessed on study groups 1,2 and 3).
Exploratory Immunogenicity Objectives	**Exploratory Immunogenicity Study Outcomes**
• To assess the HAI antibody responses against heterologous influenza A/H1 and H3 strains from baseline (Day 1) to approximately Days 180 and 365 after receipt of 2018/2019 Fluzone or Flublok with and without AF03 or Advax-CpG55.2 adjuvant.	• The percentages of subjects achieving HAI titer seroconversion, against heterologous H1 and H3 influenza strains on approximately Days 180 and 365 for each study group. • The percentage of subjects achieving an HAI titer ≥1:40 against heterologous H1 and H3 influenza strains at baseline (Day 1) and approximately Days 180 and 365 for each study group. • Serum HAI GMT against heterologous H1 and H3 influenza strains at baseline (Day 1) and approximately Days 180 and 365 each study group. • Ratio of serum HAI GMT against heterologous H1 and H3 influenza strains between adjuvanted and unadjuvanted study groups at baseline (Day 1) and approximately Days 180 and 365. • Geometric mean fold rise (GMFR) in HAI from baseline (Day 1) against heterologous H1 and H3 influenza strains

	at approximately Days 180 and 365 for each study group
• To assess NAI ELLA responses against heterologous N1 and N2 NA antigens from baseline (Day 1) to approximately Days 180 and 365 administration of 2018/2019 Fluzone with and without AF03 or Advax-CpG55.2 adjuvant.	• The percentage of subjects achieving seroconversion against heterologous N1 and N2 NA antigens on approximately Days 180 and 365 for study groups 1, 2 and 3. • Serum NAI GMTs against heterologous N1 and N2 NA antigens at baseline and approximately Days 180 and 365 for study groups 1, 2 and 3. • Ratio of serum NAI GMTs against heterologous N1 and N2 NA antigens between adjuvanted and unadjuvanted study groups at baseline and approximately Days 180 and 365 for study groups 1,2 and 3. • Geometric mean fold rise (GMFR) in serum NAI from baseline against heterologous N1 and N2 NA antigens at baseline and approximately Days 180 and 365 for study groups 1, 2 and 3.
• To assess the influenza neutralizing (Neut) antibody titer responses against heterologous influenza A/H1 and H3 strains from baseline (Day 1) to approximately Days 180 and 365 after administration of 2018/2019 Fluzone and Flublok with and without AF03 or Advax-CpG55.2 adjuvant.	• The percentage of subjects achieving Neut titer seroconversion against heterologous H1 and H3 influenza strains on approximately Days 180 and 365 for each study group. • Serum Neut GMT against heterologous H1 and H3 influenza strains at baseline (Day 1) and approximately Days 180 and 365 for each study group. • Ratio of serum Neut GMT against heterologous H1 and H3 influenza strains between adjuvanted and unadjuvanted study groups at baseline (Day 1) and approximately Days 180 and 365.

	• Geometric mean fold rise (GMFR) of neut antibody titers from baseline against heterologous H1 and H3 influenza strains at baseline (Day 1) and approximately Days 180 and 365 for each study group.
• To assess the longitudinal kinetics and durability of the HAI, NAI, and Neut responses against the 2018/2019 QIV strains on approximately Days 180 and 365 following receipt of the 2018/2019 Fluzone and Flublok with and without AF03 or Advax-CpG55.2 adjuvant.	• The percentage of subjects achieving HAI, NAI and Neut titer seroconversion against 2018/2019 QIV antigens and strains on approximately Days 180 and 365 for each study group (NAI titers will only be assessed on study groups 1,2 and 3). • The percentage of subjects achieving an HAI and Neut titer ≥1:40 against 2018/2019 QIV strains on approximately Days 180 and 365 for each study group (NAI titers will only be assessed on study groups 1,2 and 3). • Serum Neut, HAI and NAI GMT against 2018/2019 QIV strains on approximately Days 180 and 365 for each study group (NAI titers will only be assessed on study groups 1,2 and 3). • Ratio of serum Neut, HAI and NAI GMT against 2018/2019 QIV strains between adjuvanted and unadjuvanted study groups on approximately Days 180 and 365 (NAI titers will only be assessed on study groups 1,2 and 3). • Geometric mean fold rise (GMFR) in HAI, Neut and NAI titers from baseline (Day 1) against the 2018/2019 QIV strains at approximately Day 180 and 365 for each study group (NAI titers will only be assessed on study groups 1,2 and 3).
• To assess the HAI, Neut and NAI ELLA responses to the 2018/2019 at all timepoints and 2019/2020 QIV strains prior to and	• The percentage of subjects achieving an HAI titer ≥1:40 against 2018/2019 QIV strains at all timepoints and against 2019/2020 QIV strains at approximately D90 and D118.

approximately 28 days after vaccination with the 2019/2020 QIV in all study groups, according to serostatus at baseline and previous influenza vaccination	• The percentages of subjects achieving HAI, Neut and NAI titer seroconversion, against 2018/2019 QIV strains at approximately D29 and against 2019/2020 QIV strains at approximately D118. • Serum Neut, HAI and NAI GMTs against 2018/2019 QIV strains at all timepoints (for study groups 4, 5 and 6 NAI titers will only be assessed at D1 and D29) and against 2019/2020 QIV strains at approximately D90 and D118 (NAI titers will only be assessed on study groups 1,2 and 3). • Serum Neut, HAI and NAI GMFRs against 2018/2019 QIV strains on approximately Days 8, 29, 57, 90, 118, 180 and 365 (for study groups 4, 5 and 6 NAI titers will only be assessed at D1 and D29) and against 2019/2020 QIV strains at approximately D118 (NAI titers will only be assessed on study groups 1,2 and 3).
• To assess B Cell effector and memory responses prior to (Day 1) and following receipt of 2018/2019 Fluzone and Flublok with and without AF03 or Advax-CpG55.2 adjuvant.	• Change in the frequency of influenza specific-IgG, IgM and IgA B memory cells using multiplexed FluroSpot from baseline (Day 1) to approximately Days 29 and 90 for each study group. • Change in frequency of influenza-specific IgG, IgM and IgA effector B cells (plasmablast) using multiplexed Fluorospot from baseline (Day 1) to approximately Day 8 for each study group.
• To assess plasmablast and T follicular helper (Tfh cell responses prior to (Day 1) and following receipt of 2018/2019 Fluzone and Flublok with and without AF03 or Advax-CpG55.2 adjuvant.	• Change in the frequency of plasmablast and Tfh cells using multiparametric flow cytometry from baseline (Day 1) to approximately Day 8 for each study group.

• To assess the functional non-neutralizing Fc-effector antibody responses prior to (Day 1) and following receipt of 2018/2019 Fluzone and Flublok with and without AF03 or Advax-CpG55.2 adjuvant.	• GMT of functional non-neutralizing Fc-effector antibodies against vaccine strain antigens at baseline (Day 1) and approximately Day 29 after vaccination for each study group. • Geometric mean fold rise (GMFR) in functional non-neutralizing Fc-effector antibody titers from baseline (Day 1) against the 2018/2019 QIV strains at approximately Day 29 for each study group
• To assess responses from baseline (Day 1) in transcriptomic profiling on approximately Days 2 and 8 following receipt of 2018/2019 Fluzone and Flublok with and without AF03 or Advax-CpG55.2 adjuvant.	• Differential expression of transcription profiles comparing samples taken just prior to (Day 1) and on approximately Days 2 and 8 following receipt of the 2018/2019 QIV vaccination in at least a subset of subjects for each study group .
• To evaluate the relationship of non-neutralizing Fc-effector antibodies titers with HAI and NA responses following receipt of 2018/2019 Fluzone and Flublok with and without AF03 or Advax-CpG55.2 adjuvant.	• The association of non-neutralizing Fc-effector antibodies GMT with HAI and Neut antibody GMT, seroprotection and seroconversion rates to variant influenza strains and the 2018/2019 QIV vaccine strains.
• To describe the non-neutralizing Ab responses to different influenza HA antigens by a multiplex ELISA assay at all time points in each study group	• Quantification of HA binding antibodies against different influenza HA antigens at baseline (Day 1) and Days 8, 29, 57, 90, 118, 180 and 365 in each study group.
• To describe the NA binding antibody response to NA antigens corresponding to the vaccine strain antigens by an ELISA assay after administration of Fluzone with and	• Quantification of NA binding antibodies against influenza NA antigens corresponding to the vaccine strain antigens at baseline (Day 1), Day 29, 57, 90 and D118 in Groups 1, 2, 3. Additional studies on Days180 and 365

without AF03 or Advax-CpG55.2 adjuvant.	in Groups 1,2,3 will be contingent on seeing increased seroconversion rates to homologous vaccine strain antigens

Description of Study Design:

This is a Phase I, randomized, double blinded, clinical trial in up to 240 males and non-pregnant females, 18-45 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 either the 2018/2019 Fluzone or Flublok Quadrivalent Influenza Vaccines (QIV), manufactured by Sanofi Pasteur (SP) given without adjuvant or with one of two adjuvant formulations, AF03 (SP) or Advax-CpG55.2 (Vaxine Pty Ltd). Fluzone is a quadrivalent split virion inactivated vaccine whereas Flublok is a quadrivalent influenza vaccine that contains recombinant hemagglutinin proteins. AF03 is a squalene-based emulsion adjuvant, whereas Advax-CpG55.2 is a combination adjuvant comprised of delta inulin and the oligonucleotide, CpG55.2. Enrollment will occur in the second and third quarters of calendar year 2019 to allow antibody titers to previous doses of 2018/2019 IIV to wane.

Subjects will be stratified by prior receipt of licensed, seasonal influenza vaccine (defined as receipt of at least one of the 2017/2018 and/or 2018/2019 influenza vaccines) and will be randomly assigned to 1 of 6 treatment arms to receive a single dose of one of the two seasonal 2018/2019 QIV vaccine formulations with or without one of the two adjuvants (Day 1). On approximately Day 90, each subject will receive a single dose of the seasonal 2019/2020 influenza vaccine. Groups 1, 2 and 3 will receive 2019/2020 Fluzone QIV and Groups 4, 5 and 6 will receive 2019/2020 Flublok QIV.

To determine early safety signals for this Phase I study, enrollment will proceed in a staged fashion for the first 6 sentinel subjects. The first six subjects will be randomized and vaccinated with one each from Groups 1-6. These six subjects will be followed through Day 8. If any of the pre-specified halting rules for the sentinel subjects occur, the study will be halted and reviewed by the DSMB. If no pre-specified safety signals are encountered enrollment will proceed.

It is anticipated that both adjuvant formulations (AF03 and Advax-CpG55.2) will be available at the start of study enrollment. However, if the Advax–CpG55.2 is not available, the study will proceed only with groups 1, 2, 4 and 5 open for enrollment for the remaining subjects (up to 240, 60 per group). For the sentinel subjects, one subject from groups 1, 2, 4 and 5 will be enrolled and followed through Day 8. If any of the pre-specified halting rules for sentinel subjects occur, the study will be halted and reviewed by the DSMB. If no pre-specified events occur, randomization will proceed in groups 1, 2, 4 and 5 for the remaining subjects.

The DSMB will review the data when the 8-day reactogenicity and clinical safety laboratory data following the first study vaccination are available for 50% of study

subjects. Enrollment will not be paused for this review. An additional scheduled DSMB review will occur when all HAI, NAI and Neut data for Day 1, and Day 29 and safety data through Day 57 following the first study vaccination, are available.

Reactogenicity will be measured by the occurrence of solicited injection site and systemic reactions from the time of the first study vaccination through Day 8. Unsolicited non-serious adverse events (AEs) will be collected from Day 1 through approximately Day 29. Serious adverse events (SAEs), Adverse Events of Special Interest (AESIs) including reports of tearing, dry mouth, dry eyes 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 study vaccination through approximately 12 months after the first study vaccination. Clinical safety laboratory evaluations (hematology and chemistry) will be performed at screening, immediately prior to the first study vaccination and at approximately Day 8.

Only pharmacy personnel, the Emmes unblinded team and an unblinded vaccinator will have access to the study codes; all other study personnel will be blinded. Immunogenicity testing will include performing serological assays to assess hemagglutination inhibition (HAI), neutralizing (Neut) and neuraminidase inhibition (NAI) titers at multiple time points following both study vaccinations. Antibody responses will be determined for both influenza vaccine strains and heterologous influenza strains. In addition, whole blood transcriptomics and peripheral blood mononuclear cells (PBMCs) will be used to determine transcriptional profiling and broad immunologic responses and to associate these responses with serological antibody responses described above in each of the treatment arms. Immunologic responses will include longitudinal assessments of the kinetics, magnitude, specificity, and/or quality of influenza-specific memory B cells, plasmablasts, and circulating T follicular helper (T_{FH}) cells and non-neutralizing antibody responses to HA and NA antigens

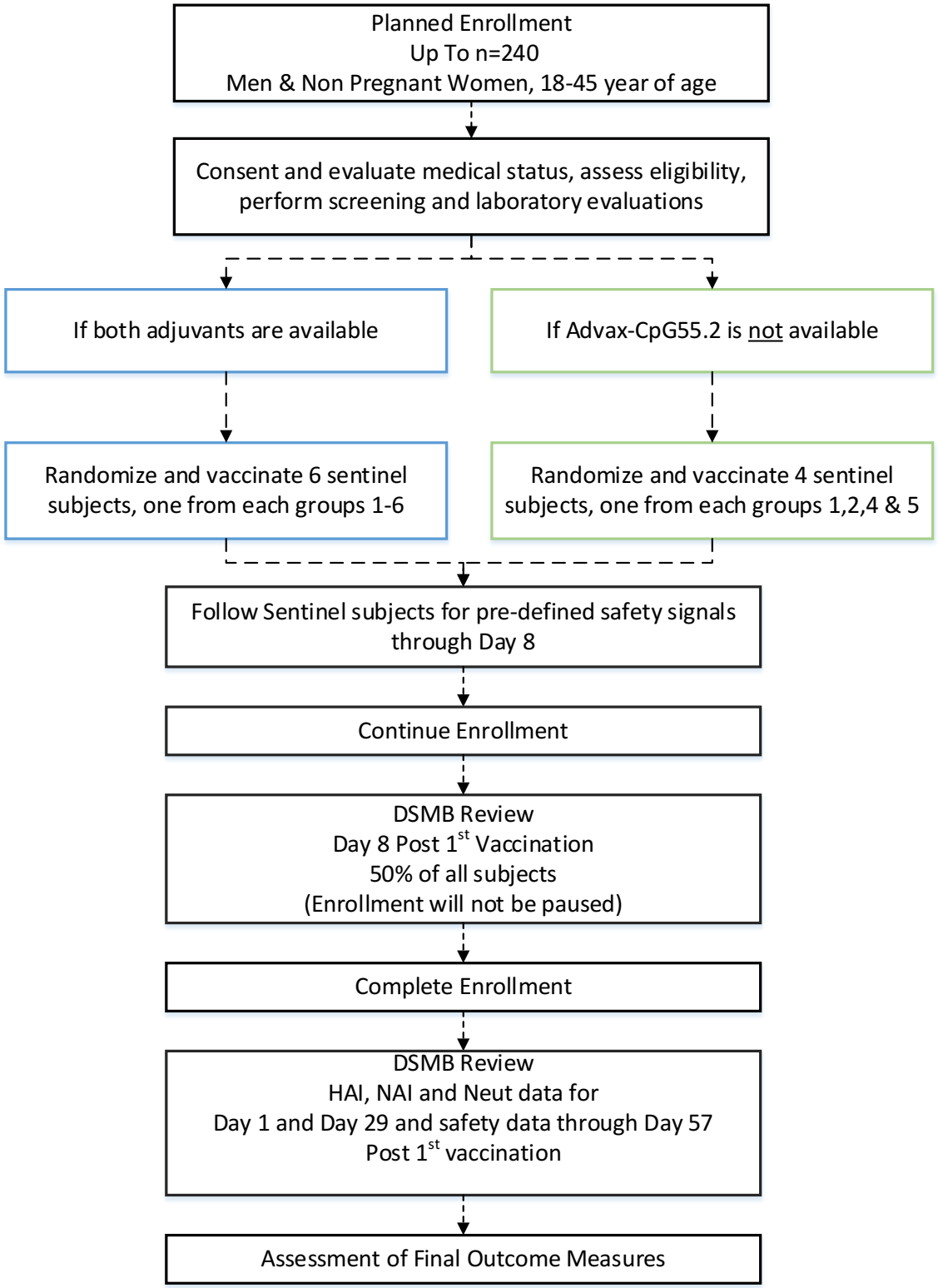
Table 2: Study Design

		Day 1		Day 90
Study Group	**N**	**Study Vaccine**	**Adjuvant**	**Seasonal Vaccine**
1	**40**	**Fluzone 2018/2019 QIV**	None	Fluzone 2019/2020 QIV
2	**40**	**Fluzone 2018/2019 QIV**	AF03	Fluzone 2019/2020 QIV
3[A]	**40**	**Fluzone 2018/2019 QIV**	Advax-CpG55.2	Fluzone 2019/2020 QIV
4	**40**	**Flublok 2018/2019 QIV**	None	Flublok 2019/2020 QIV
5	**40**	**Flublok 2018/2019 QIV**	AF03	Flublok 2019/2020 QIV
6[A]	**40**	**Flublok 2018/2019 QIV**	Advax-CpG55.2	Flublok 2019/2020 QIV
	Total N= 240 [A]			

Note: Cohorts will be enrolled simultaneously. Randomization at each site will be stratified by 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).

[A] If Advax-CpG55.2 is not available, the study will proceed only with groups 1, 2, 4 and 5 open for enrollment for the remaining subjects (up to 240, 60 per group) in groups 1, 2, 4 and 5.

Figure 1: Schematic of Study Design



1 KEY ROLES

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Statistical and Data Coordinating Center:	The Emmes Company, LLC
Clinical Materials Services:	Fisher BioServices
Central (Clinical) Laboratory:	PPD Global Central Laboratories
HAI, NAI, Neut Antibody, Cellular Immunology, Transcriptomics and Additional Serological Assays Laboratory:	Sanofi Pasteur

2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Influenza is a common acute viral respiratory illness. Seasonal influenza occurs annually, and in the United States it causes an estimated 100,000 to 600,000 hospitalizations annually and up to 50,000 deaths a year [1]. Use of influenza vaccines is the primary means for preventing influenza. Current licensed inactivated influenza vaccines (IIVs) are good for preventing influenza but are less effective than desirable. Meta-analyses examining controlled trials comparing seasonal IIV to no vaccine for preventing laboratory-confirmed influenza illness have shown remarkable variability between different seasons ranging from 16%-76% with improved, though still imperfect, efficacy seen when the IIV strains matched the circulating strains [2]. Others have evaluated the effectiveness of IIV in preventing severe influenza hospitalizations and found a pooled efficacy of 51% in adults aged 18-64 and 37% in adults 65 years of age or older [3].

Various formulations of IIV have been approved for use in the United States. Most vaccines belong to the inactivated, split virus family of vaccines that are produced from influenza viruses grown in embryonated chicken eggs or cell lines that then undergo chemical disruption and purification to produce the antigens included in the vaccine. These vaccines include not only the immunodominant hemagglutinin protein (HA) from influenza, but also smaller quantities of neuraminidase proteins (NA). Fluzone belongs to this family of IIV. More recently FDA has approved Flublok, which is also a non-replicating vaccine, but the manufacturing process and subsequent antigen composition of the vaccine is quite different from that seen with the split virus family of vaccines. Flublok contains only recombinant HA proteins (rHA) produced in an insect cell line using a baculovirus vector that encodes the influenza HA gene. The rHAs are purified from the cells and used to create the Flublok vaccine.

Serum IgG antibody to the influenza virus HA, the major component of inactivated subunit and split virus vaccines, has a major role in protective immunity to influenza virus infection [4]. Resistance to infection with seasonal influenza virus strains correlates directly with both serum hemagglutination inhibition (HAI) and neutralizing (Neut) antibody levels, and measurements of serum HAI and Neut antibodies are used routinely to assess the immunogenicity of both seasonal and pandemic IIVs. Recent data also support an important role for neuraminidase inhibiting (NAI) antibodies in protection against disease [4]. In a recent human influenza challenge study, serum NAI antibody levels were also identified as an independent correlate of protection against

influenza illness [5]. Cellular immunity also can have a role in preventing influenza-associated illness [6].

Several approaches have been used to increase the immunogenicity of IIVs. Standard-adult dose seasonal IIVs contain 15 mcg of HA antigen per seasonal influenza vaccine strain. Clinical studies evaluating increased HA-containing influenza vaccines have shown dose-related increases in serum and mucosal antibody responses [7]. 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.

The inclusion of an adjuvant provides another mechanism to improve the immune response to IIV antigens. The addition of MF59, a squalene-based, oil-in-water emulsion, to IIV has been shown to increase HAI titers to the homologous vaccine strains and also to induce cross-reactive HAI antibodies that bind drifted seasonal influenza viruses. MF59-adjuvanted seasonal IIV was approved for use in the elderly in Italy in 1997. Studies have typically shown the MF59 adjuvanted groups produce more local vaccination site tenderness and inflammation, but most events are mild-moderate [8]. Many studies were subsequently performed in other age groups and led to the approval of two MF59- adjuvanted pandemic 2009 H1N1 vaccines for use in children and all adults in 2009 [9]. Today 38 countries have approved the use of MF59-adjuvanted seasonal trivalent IIV, now called Fluad® (Fluad), and many allow use in all age groups. In 2015, the U.S. FDA approved Fluad, though it restricted the use to adults ages 65 and older.

More recently, studies have explored the use of adjuvants to enhance the antibody responses to the much less immunogenic novel avian strains of influenza virus such as A/H5N1 and A/H7N9. AS03 is a squalene-based, oil-in-water emulsion that includes □-tocopherol. Both AS03 and MF59 have resulted in increased antibody responses to IIVs containing novel HAs[9]. Studies have shown that the inclusion of these two adjuvants can reduce the antigen dose needed to achieve higher HAI and neutralizing titers and the titers are substantially greater than those generated with unadjuvanted formulations of vaccine [10].

Given the fact that the MF59 and AS03 adjuvants were dose-sparing and improved the antibody responses generated when added to otherwise poorly immunogenic influenza vaccines, they are considered to be of critical importance for pandemic response planning. 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.

What has become apparent is that even modest changes to adjuvant formulations can modulate immune responses and different adjuvants work better for certain antigens. Immunological

protection for some pathogens requires cellular immune responses while others respond predominantly to humoral immune responses. Adjuvants in development or in use include a large variety of compounds including aluminum salts, oil emulsions (such as MF59 and AS03 mentioned above), saponins, immune-stimulating complexes, liposomes, microparticles, nonionic block copolymers, polysaccharides, cytokines and bacterial derivatives[11-16]. Given the relatively modest effectiveness of influenza vaccines, these vaccines serve as an important target for testing new adjuvants. Clearly, both immunogenicity as well as safety will be important factors as new adjuvanted influenza vaccines are reviewed for licensure.

AF03 is a squalene emulsion-based adjuvant that utilizes an alternative manufacturing process that involves phase inversion temperature emulsification and incorporates two non-ionic surfactants [17, 18]. During the 2009 H1N1 pandemic, Sanofi Pasteur created an AF03 adjuvanted A/H1N1 pandemic influenza vaccine (Humenza™) and performed multiple clinical trials to support the licensure of the vaccine in the European Union. This included trials in children 6 months-17 years of age, adults 18-60 years of age and adults above 60 years of age. There is one published study that evaluated children ages 6 months to 17 years who were enrolled in a trial comparing AF03- adjuvanted and non-adjuvanted pandemic H1N1 influenza vaccine. The youngest children, those ages 6-35 months, showed significantly improved antibody titers with the adjuvanted vaccine compared to the unadjuvanted vaccine and the adjuvanted vaccine led to better antibody persistence [18]. AF03 clinical trials have also been performed with A/H5N1 vaccine [19] (SP AF03 IB).

To further assess the safety of AF03 when mixed with licensed Fluzone and FluBlok QIV, Sanofi conducted a recent GLP toxicology study in rabbits. The objective of the GLP toxicology study was to determine the systemic toxicity and the local tolerance of Fluzone and Flublok Quadrivalent *influenza* vaccines adjuvanted with AF03 in New Zealand White (NZW) rabbits following three 0.75 mL IM administrations at 2-week intervals (on D1, D15, and D29) in the dorsal lumbar muscles.

Three groups of 10 males and 10 females were given either Fluzone or Flublok vaccine (at 15µg or 45µg of HA per influenza virus strain per dose) adjuvanted with AF03 (12.5 mg squalene per dose), or a saline control (NaCl 0.9%). Mortality, clinical signs and local reactions, ophthalmology, body weight, food consumption, clinical pathology, and immunogenicity were investigated. Animals were euthanized either 2 or 28 days after the third injection (on D31 or D57). A microscopic examination was performed on the preserved tissues from all animals as per the WHO guidelines document on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines (2013).

AF03-adjuvanted Fluzone and Flublok vaccines were clinically well tolerated in the rabbit with no unscheduled deaths, no adverse clinical signs, no ophthalmological findings, and no adverse

effects on body weight or food intake. Immunogenicity results demonstrated a good humoral response after vaccination in all treated groups. Injections of both vaccines showed reversible minimal to moderate inflammatory changes at the injection sites associated with related lymphoid hyperplasia in lymph nodes and spleen, as well as increase in white blood cell counts and treatment-related increase in C reactive protein, fibrinogen and globulin levels. All changes showed either complete or partial recovery by the end of the 4-week observation period and were considered as related to the pharmacology activity of the adjuvanted vaccines, but non-adverse.

Advax™ is yet another adjuvant that has been tested as a component to inactivated seasonal and pandemic influenza vaccines including 2009 H1N1 and H5N1 vaccine antigens. Advax is a polysaccharide adjuvant that contains particles of semi-crystalline delta inulin, a plant based carbohydrate [13]. In the mid-1980s the studies demonstrated that semi-crystalline particles of inulin activated complement through the non-classical pathway and could act as a vaccine adjuvant [20]. Advax, a more temperature stable delta inulin isoform created by Vaxine Pty Ltd has been found to have improved adjuvant potency in animal models and humans when combined with a number of vaccines including Japanese encephalitis, West Nile virus, HIV, influenza , RSV, SARS coronavirus, tuberculosis, Listeria, anthrax, chlamydia and hepatitis B [13],[21-34]. This adjuvant enhances both humoral and cellular immunity to co-administered antigens and induces a potent antigen-specific CD4+ and CD8+ memory T cell response as well as enhanced production of antigen specific IgM, IgG and IgA [35]. Advax adjuvant has been shown to enhance vaccine immunogenicity and protection through stimulation of both cellular and humoral immune pathways when combined with inactivated influenza virus (in mice, rats and sheep), inactivated avian H5N1 influenza (in mice and ferrets) and recombinant HA antigen from H1, H5 and H7 strains of influenza virus (in mice, rabbits, and humans) [36-42].

Over 10 human trials have been conducted with Advax, including several that evaluated Advax adjuvanted IIV for seasonal influenza and 2009 pandemic H1N1, in Australia and Europe involving over 2000 subjects. The first in man Advax-adjuvanted seasonal trivalent IIV (IIV3) vaccine study showed that the adjuvant given with $1/10^{th}$ the dose of the standard IIV vaccine generated equivalent seroprotection rates and GMTs compared to the full standard dose of unadjuvanted IIV3 vaccine [37]. There were no significant differences seen in solicited, unsolicited or serious adverse events, though there was a trend toward reduced incidence of fever and arthralgias in the reduced IIV3 dose Advax-adjuvanted arm as compared to the full dose standard IIV3. A rHA vaccine from the pandemic 2009 H1N1 influenza strain adjuvanted with Advax also showed significantly improved HAI and Neutralising antibody titers, seroconversion and seroprotection rates when compared to unadjuvanted vaccine, with no increase in systemic adverse events when compared to the unadjuvanted vaccine, and an unexpected but significant reduction in post-immunization headaches in the week following immunization in the Advax-adjuvanted arms [36].

Unmethylated CpG oligonucleotides have been found to serve as Toll-like Receptor (TLR) 9 agonists that enhance antigen-specific immune responses and induce pro-inflammatory cytokines particularly IL-12, which can enhance downstream production of Th1 cytokines that promote survival and proliferation of Th1 cells and can activate T_{FH}, which enhance B cell immunoglobulin production. Thus, CpG enhances both cellular and humoral immune responses. A range of CpG oligonucleotides have been evaluated as adjuvants either alone or in combination with alum adjuvants, in human trials of vaccines against infectious disease (hepatitis B, influenza, anthrax, malaria, and HIV), cancer and allergy.

Studies have been performed to determine whether the addition of CpG to Advax can improve immune responses to various vaccine antigens. In a mouse study evaluating a candidate *Mycobacterium tuberculosis* vaccine, the addition of CpG246.1 to Advax enhanced the generation of chemoattractants and resulted in a rapid influx of monocytes and neutrophils to the site of vaccination with significant early priming of vaccine antigen specific CD4+ T cells [33]. A ferret study evaluated Advax-CpG246.1 and Advax-alone adjuvanted H5N1 vaccine. Advax-CpG246.1 adjuvant enhanced HAI titers and protection from influenza virus challenge over and above Advax adjuvant alone when combined with influenza H5N1 vaccine [42]. Phase I trials have been conducted to evaluate Panblok-H5® vaccine alone or in combination with Advax-CpG246.1 adjuvant. An interim analysis was performed on subjects who completed both immunizations and had blood samples drawn at 4 weeks. The highest levels of H5 HAI titers were in the Advax-CpG246.1 group; these were statistically improved over unadjuvanted vaccine (see Advax-CpG IB). A similar Phase 1 trial was conducted evaluating Panblok-H7® alone or with Advax or Advax-CpG246.1 adjuvant. The preliminary data indicates that the immune responses are similar to those seen in the H5 rHA vaccine trial, with the highest HAI titers against H7 in the Advax-CpG246.1 adjuvanted arm, versus very low or undetectable HAI titers in the Panblok-H7® alone arm and intermediate results in the Advax arm (see Advax-CpG IB). The version of CpG oligonucleotide that Vaxine used in Advax-CpG clinical trials to date is a 24-mer class B CpG oligonucleotide with a phosphorothioate backbone called CpG246.1. Vaxine has subsequently further optimized the CpG nucleotide sequence to maximize its activity for both human and mouse TLR9, resulting in the oligonucleotide CpG55.2. CpG55.2 is also a 24-mer class B CpG oligonucleotide with a phosphorothioate backbone, however, the sequence order of the nucleotides is different between CpG55.2 and CpG246.1.

To further assess safety of the Advax-CpG55.2 combination adjuvant when mixed with licensed Fluzone and FluBlok QIV, Sanofi conducted a recent GLP toxicology study in rabbits. The objective of the GLP toxicology study was to determine the systemic toxicity and local tolerance of Fluzone and Flublok Quadrivalent influenza vaccines adjuvanted with Advax-CpG55.2 in NZW rabbits following three 1 mL IM administrations at 2-week intervals (on D1, D15, and D29) in the dorsal lumbar muscles.

Four groups of 10 males and 10 females were given either Fluzone or Flublok vaccine (at 15 µg or 45 µg of HA per influenza virus strain per dose) adjuvanted with Advax-CpG55.2 (20 and 0.2 mg per dose, respectively), Advax-CpG55.2 alone at the same dose level or a saline control (NaCl 0.9%). Mortality, clinical signs and local reactions, ophthalmology, body weight, food consumption, clinical pathology, and immunogenicity were investigated. Animals were euthanized either 2 or 28 days after the third injection (on D31 or D57). A microscopic examination was performed on the preserved tissues from all animals as per WHO guidelines (2013).

Advax-CpG55.2-adjuvanted Fluzone and Flublok vaccines were clinically well tolerated in the rabbit with no unscheduled deaths, no adverse clinical signs, ophthalmological findings, and no effects on body weight or food intake. Immunogenicity results demonstrated a good humoral response after vaccination in all vaccinated groups. Injections of both vaccines showed reversible inflammatory changes at the injection sites associated with related lymphoid hyperplasia in lymph nodes and spleen, as well as increase in C-Reactive Protein and fibrinogen levels. All changes showed either complete or partial recovery by the end of the 4-week observation period and were considered as related to the pharmacology activity of the adjuvanted vaccines, but non-adverse.

The proposed trial will be the first time that an Advax-CpG formulation incorporating CpG55.2 in place of CpG246.1 will be tested in humans.

2.2 Scientific Rationale

Seasonal influenza vaccines have variable efficacy. Efficacy can be reduced when the vaccine strains have mismatched antigenic profiles as compared to the circulating strains of influenza virus. Additionally, populations can have variable efficacy based on the immunological sequence of prior exposure to influenza infections or vaccines. Adjuvants provide a promising strategy to enhance the humoral immune responses to influenza proteins and may enhance the cellular memory responses, as well. Two new adjuvants are being evaluated that show promise in animal studies (Advax-CpG55.2 and AF03) and early human trials (AF03). These two products have been tested predominantly as adjuvants for novel avian influenza strains that show poor immunogenicity. However, there is great need to improve vaccine efficacy that can overcome the problems of antigenic drift, immunosenescence and prior immunological priming.

The goal of this clinical trial is to assess in healthy adults, 18-45 years of age, the safety, reactogenicity and immunogenicity of one dose of 2018/2019 Quadrivalent Influenza Vaccine (either Fluzone or Flublok) administered intramuscularly (IM) with or without one of two adjuvants (AF03 or Advax-CpG55.2). The study will evaluate the traditional HAI and Neut

responses among groups, but also will explore additional immunological parameters. Since antibodies targeting the NA may represent an independent correlate of protection against influenza infection [43] [5], we plan to assess the NAI responses in each group. The longitudinal kinetics and durability of HAI, Neut, and NAI responses will be evaluated for one year following vaccination.

This clinical trial will also assess cellular correlates of immunity to influenza including memory B cell populations, plasmablasts, T_{FH} cells, functional non-neutralizing Fc-effector antibodies, as well as determine the transcriptional profiling responses following vaccination.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

The potential risks of participating in this trial are those associated with having blood drawn, the IM injection, possible reactions to the Fluzone or Flublok QIV, with or without AF03 or Advax-CpG55.2 adjuvant, and breach of confidentiality.

Drawing blood may cause transient discomfort and fainting and lead to or exacerbate iron deficiency in those who are not anemic. Fainting is usually transient and managed by having the subject lie down and elevating 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) and clinical safety labs for white blood cells (WBC), hemoglobin (Hgb), platelets (PLT), alanine aminotransferase (ALT), total bilirubin (T. Bili), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP) serum lipase and serum amylase and creatinine (Cr). Only subjects with a stable health history, physical exam and laboratories that fall within acceptable range (see Section 5.1.1) will proceed to vaccination.

Fluzone and Flublok Vaccines

The 2018/2019 and 2019/2020 QIV products used in this study are approved by the FDA for active immunization against disease caused by influenza viruses contained in the vaccine.

Occasionally, adult recipients of unadjuvanted licensed, inactivated influenza vaccines (IIVs) may develop influenza-like reactions, such as fever, feverishness, fatigue, malaise, myalgia, arthralgia, headache, and/or nausea. Some subjects may develop reactions at the injection site, including pruritus, ecchymosis, erythema, induration, edema, 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.

During the clinical development of Flublok, which is a recombinant influenza vaccine (RIV), both local and systemic reactogenicity symptoms were generally similar in frequency and severity to those observed with the active control vaccines (trivalent or quadrivalent influenza vaccines, TIV or QIV) in adults. The only SAEs that were considered related or possibly related to Flublok in any of the trials were one case of vasovagal syncope (quadrivalent RIV, within 20 minutes post-vaccination, attributed to the injection process rather than the vaccine material) and one case of non-infectious pericardial effusion (trivalent RIV, 11 days post-vaccination).

Serious immediate reactions, such as hypersensitivity, or delayed reactions, such as Guillain-Barré syndrome, have not been observed in the clinical trials with any formulations of rHA vaccines.

In addition, post-marketing surveillance of the seasonal IIVs indicates autoimmune and other disorders as potential risks; 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 hives, angioedema, bronchospasm, tachycardia, or hypotension. If these reactions occur, they can usually be stopped by the administration of emergency medications by the study personnel. As with any vaccine or medication, there is a very small chance of a death, although researchers do not expect this to occur.

During the swine influenza (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 [44]. Interestingly, although vaccination rates have increased in the last 10 years, the numbers of reported cases of vaccine-associated GBS have declined [45]. 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 [46]. 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 [47-49]. 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) [50]. An international collaboration study also supported a conclusion of an association between 2009 A/H1N1 vaccination and GBS [51].

AF03

Over 1500 people have been evaluated in clinical trials conducted in the European Union and the US evaluating inactivated, monovalent H5N1 or H1N1 influenza vaccine adjuvanted with AF03. (SP AF03 IB)

In Phase I and Phase II clinical trials in adults, the most frequently observed local reactions were pain, induration and erythema and the most frequently reported solicited systemic reactions in all groups and for each injection were headache and myalgia. Most local and systemic reactions generally appeared on the day following vaccination and disappeared within 3 days without medication use. The addition of AF03 has been associated with a higher incidence of local reactions, mainly characterized by injection site pain and induration, compared to non-adjuvanted vaccine. The addition of AF03 was associated with an increased incidence of systemic reactions when compared to unadjuvanted vaccine in adults.

Some systemic adverse events have been rarely observed concomitantly with the administration of vaccines from other manufacturers containing oil-in-water adjuvants similar to AF03. These systemic adverse events include autoimmune diseases and demyelinating neurological disorders. No causal relationship has been established between these observations and oil-in-water adjuvants. To date, these events have not been observed with AF03 adjuvanted vaccines.

Animal toxicology studies following administration of high doses of AF03 and AF04 have shown increased single cell apoptosis or necrosis in acinar tissues including the lacrimal gland

and the exocrine pancreas in the rabbit model and the parotid glands in rats. These findings were observed only at high doses, of low severity and reversible, they were therefore not considered clinically significant.

Advax-CpG55.2

The clinical experience with combination adjuvants combining Advax and TLR9 agonist oligonucleotides such as CpG remains limited. However, approximately 400 exposures in approximately 160 adult humans to an earlier generation combined formulation of Advax with CpG246.1, a class B CpG oligonucleotide similar to CpG55.2, have been evaluated in Phase I trials with various investigational vaccines. When formulated with influenza vaccines Advax-CpG246.1 induced similar types of local and systemic reactions to those seen in subjects receiving unadjuvanted IIV's which mimicked influenza-like reactions, with symptoms such as feverishness, fatigue, malaise, myalgia, arthralgia, headache, and/or nausea. An increase in local injection site reactions, including pruritus, ecchymosis, erythema, induration, edema, pain, and/or tenderness is typically seen when using vaccine adjuvants, and was similarly observed in trials of Advax-CpG246.1 adjuvanted vaccines, but these local reactions were predominantly mild in severity and were self-limiting. Most of these reactions peaked in intensity in the first 24 hours after vaccination and resolved without treatment within 1 or 2 days. The most common solicited systemic adverse reaction in the first seven days post-immunization was headache, which affected 20-35% of participants. The next most common solicited systemic adverse reactions in the first seven days post- immunization were muscle ache (~20%), fatigue (~10%) and shivering and chills (~5%). The frequency of unsolicited adverse events was not significantly different between the Advax-CpG, Advax and non-adjuvanted groups. Analgesics (e.g., acetaminophen, ibuprofen or similar NSAIDs) and rest generally relieved or lessened these reactions

Risks of Genetic Testing

Genetic data and health information will be stored and shared with other researchers through a controlled-access repository, such as dbGaP. There may be a risk that information resulting from research genetic testing could be misused for discriminatory purposes. However, state and federal laws provide protections against genetic discrimination. Researchers will need to maintain confidentiality in order to be granted access to genetic information.

2.3.2 Known Potential Benefits

The unadjuvanted seasonal QIVs are known to stimulate HAI antibody titers that can reduce the likelihood of influenza virus infection and/or reduce the likelihood of severe influenza illness.

The inclusion of an adjuvant, either AF03 or Advax-CpG55.2, could improve the titers of protective antibodies. However, the timing of the start of this study is designed to coincide with a time when influenza virus is unlikely to be circulating so it is not clear that an individual would receive any benefit to receiving 2018/2019 QIV. All participants will receive a dose of 2019/2020 QIV which may provide protection from influenza for the 2019/2020 influenza season. There may also be benefits to society through the improvement of our understanding of these two new adjuvants and how they affect the immune response to seasonal influenza vaccine.

3 STUDY OBJECTIVES AND OUTCOME MEASURES

Refer to Table 1: Study Objectives and Outcome Measures

4 STUDY DESIGN

This is a Phase I, randomized, double blinded, clinical trial in up to 240 males and non-pregnant females, 18-45 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 either the 2018/2019 seasonal Fluzone or Flublok QIV manufactured by Sanofi Pasteur (SP) given without adjuvant or with one of two adjuvant formulations, AF03 (SP) or Advax-CpG55.2 (Vaxine Pty Ltd as manufactured by Sypharma and Nikko Denka Avecia). Fluzone is a quadrivalent split virion inactivated vaccine, whereas Flublok is a quadrivalent influenza vaccine that contains recombinant hemagglutinin proteins. AF03 is a squalene-based emulsion adjuvant, whereas Advax-CpG55.2 is a combination adjuvant comprised of Advax (delta inulin) and the oligonucleotide, CpG55.2. Enrollment will occur in the second and third quarters of calendar year 2019 to allow antibody titers to previous doses of 2018/2019 IIV to wane.

Subjects will be stratified by prior receipt of licensed, seasonal influenza vaccine (defined as receipt of at least one of the 2017/2018 and/or 2018/2019 influenza vaccines) and will be randomly assigned to 1 of 6 treatment arms to receive a single dose of one of the two seasonal 2018/2019 QIV vaccine formulations with or without one of the two adjuvants (Day 1). On approximately Day 90, each subject will receive a single dose of the seasonal 2019/2020 QIV. Groups 1, 2 and 3 will receive 2019/2020 Fluzone QIV and Groups 4, 5 and 6 will receive 2019/2020 Flublok QIV.

To determine early safety signals for this Phase I study, enrollment will proceed in a staged fashion for the first 6 sentinel subjects. The first six subjects will be randomized and vaccinated with one each from Groups 1-6. These six subjects will be followed through Day 8. If any of the pre-specified halting rules occur, the study will be halted and reviewed by the DSMB. If no pre-specified safety signals are encountered enrollment will proceed.

It is anticipated that both adjuvant formulations (AF03 and Advax-CpG55.2) will be available at the start of study enrollment. However, if the Advax-CpG55.2 is not available, the study will proceed only with groups 1, 2, 4 and 5 open for enrollment for the remaining subjects (up to 240, 60 per group). For the sentinel subjects, one subject from groups 1, 2, 4 and 5 will be enrolled and followed through Day 8. If any of the pre-specified halting rules occur, the study will be halted and reviewed by the DSMB. If no pre-specified events occur, randomization will proceed in groups 1, 2, 4 and 5 for the remaining subjects.

The DSMB will review the data when the 8-day reactogenicity and clinical safety laboratory data following the first study vaccination is available for 50% of study subjects. Enrollment will not be paused for this review. An additional scheduled DSMB review will occur when all HAI, NAI and Neut data for Day 1, and Day 29 and safety data through Day 57 following the first study vaccination, are available.

Reactogenicity will be measured by the occurrence of solicited injection site and systemic reactions from the time of the first study vaccination through Day 8. Unsolicited non-serious adverse events (AEs) will be collected from Day 1 through approximately Day 29. Serious adverse events (SAEs), AESIs including reports of tearing, dry mouth, dry eyes and MAAEs, including NOCMCs and PIMMCs, will be collected through approximately 12 months after the first study vaccination. Clinical safety laboratory evaluations (hematology and chemistry) will be performed at screening, immediately prior to the first study vaccination and approximately Day 8.

Only pharmacy personnel, the Emmes unblinded team and an unblinded vaccinator will have access to the study codes all other study personnel will be blinded. Immunogenicity testing will include performing serological assays to assess hemagglutination inhibition (HAI), neutralizing (Neut) and neuraminidase inhibition (NAI) titers at multiple time points following study vaccination. Antibody responses will be determined for both influenza vaccine strains and heterologous influenza strains. In addition, whole blood transcriptomics and peripheral blood mononuclear cells (PBMCs) will be used to determine transcriptional profiling and broad immunologic responses and to associate these responses with serological antibody responses described above in each of the treatment arms. Immunologic responses will include longitudinal assessments of the kinetics, magnitude, specificity, and/or quality of influenza-specific memory B cells, plasmablasts, and circulating T follicular helper (T_{FH}) cells.

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: Adverse Events of Special Interest.

5 STUDY ENROLLMENT AND WITHDRAWAL

Up to 240 males and non-pregnant females, 18 to 45 years of age, inclusive, who are in good health and meet all eligibility criteria will be enrolled at up to 8 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 9 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 the recruitment process and 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. Are males or non-pregnant females, 18 to 45 years of age, inclusive at time of enrollment.
5. Are in good health[1].

[1] *As determined by medical history and physical examination to evaluate acute or currently ongoing chronic medical or psychiatric 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, or invasive medical procedure and no adverse symptoms that need medical intervention such as medication change/supplemental oxygen). This includes no change in chronic prescription medication, dose or 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. 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 or treatment of continued symptoms of medical diagnosis or condition. Note: Low dose topical, corticosteroids as outlined in the Subject Exclusion Criteria (see Section 5.1.2) as well as herbals, vitamins and supplements are permitted.

6. Oral temperature is less than 100.0°F.

7. Pulse is 47 to 100 beats per minute, inclusive.

8. Systolic blood pressure is 85 to 140 mmHg, inclusive.

9. Diastolic blood pressure is 55 to 90 mmHg, inclusive.

10. Screening laboratories (ESR, WBC, Hgb, PLTs, ALT, T. Bili, AST, GGT, ALP serum lipase, serum amylase and Cr) are within acceptable parameters [%]

    [%] *ESR must be below 30 mm/hr; WBC >3.90 K/MM3 and <10.60 K/MM3; Hgb ≥11.5 g/dl (women) or ≥12.5 g/dl (men); PLTs (EDTA) 140-415 K/MM3;PLTs (Citrate) 125-325 K/MM3 ALT ≤43U/L (women) or ≤60 U/L (men); T Bili ≤1.20 mg/dl; Cr <1.1mg/dl (women) or < 1.4 mg/dl (men); AST 10-36 U/L (women) or 10-43 U/L (men); GGT 5--32 U/L (women) or 10-49 U/L (men); ALP 30-115 U/L (women) or 43-115 U/L (men); lipase 13-60 U/L; amylase (Total) 35-121 U/L, for subjects to qualify for randomization and vaccination.*

11. Women of childbearing potential[2] must use an acceptable contraception method[3] from at least 30 days before the first study vaccination until 60 days after the second study vaccination.

    [2]*Not sterilized via bilateral oophorectomy, tubal ligation/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, full abstinence from sexual intercourse with a male partner, monogamous relationship with vasectomized partner who has been vasectomized for 180 days or more and shown to be azoospermic prior to the subject receiving the 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").*

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

13. For a woman with potential to become pregnant, she understands that in the event of pregnancy during the study she will be approached to enroll in the Sanofi Pregnancy Registry.

14. Must agree to have residual specimens (i.e. residual/excess of per protocol specifications) (see Section 14.8).

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

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 or recently active (12 months) 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 history of GBS.

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

11. Have a history of PIMMCs[6].

[6]*Refer to Appendix B: Adverse Events of Special Interest*

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

13. Have any diagnosis, current or past, of schizophrenia, bipolar disease or other psychiatric diagnosis that may interfere[7] with subject compliance or safety evaluations.

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

14. Have been hospitalized for psychiatric illness, history of suicide attempt, or confinement for danger to self or others within 5 years prior to study vaccination.

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

16. Have taken high-dose inhaled corticosteroids[8] within 30 days prior to 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.*

17. Received or plan to receive a licensed, live vaccine (excluding all licensed, seasonal LAIVs) within 30 days before or after the study vaccination.

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

19. Have received any 2018/2019 seasonal influenza vaccine within the 6 months prior to enrollment.

20. Plans to receive any 2019/2020 seasonal influenza vaccine within approximately 90 days of receipt of the first study vaccination.

21. Have a known history of documented influenza infection within the past 6 months.

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

23. Received an experimental agent[9] within 30 days prior to the study vaccination or expect to receive another 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 first study vaccination.*

24. 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 first study vaccination.*

25. Female subjects who are breastfeeding or plan to breastfeed from the time of the first study vaccination through 30 days after the last study vaccination.

26. Plan to travel outside the US (continental US, Hawaii and Alaska) from the time of study vaccination through approximately 90 days after the first study vaccination.

27. Planning to donate blood within 4 months following first vaccination.

5.1.3 Exclusion Criteria for Second Study Vaccination

All study participants will be expected to receive the second study vaccination except under the circumstances listed below. The second study vaccination will not be administered to a subject if any of the following criteria are met:

- Meets the contraindication on the package insert to receipt of licensed influenza vaccine.
- As deemed necessary by the site principal investigator or appropriate sub-investigator for noncompliance or other reasons.
- Subject refusal of further study vaccination.
- Withdrawal of consent.
- Subject is lost to follow-up.
- Termination of this trial.
- New information becomes available that makes further participation unsafe.

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) Advantage eClinical^{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 in the electronic data capture system. If all study adjuvants are available at the time of study start, the subject will be enrolled and randomly assigned with equal allocation (1:1:1:1:1:1) 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). All subjects will receive a licensed 2019/2020 QIV on approximately Day 90.

If the Advax-CpG55.2 components are not available groups 1, 2, 4, and 5 will be enrolled, and subjects (up to 240) will be randomized with equal allocation (1:1:1:1) to these 4 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). Enrollment of subjects will be done online using the enrollment module of Advantage eClinical^{SM}. The randomization code will be prepared by statisticians at the SDCC and included in the enrollment module for this trial. Advantage eClinical^{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 Advantage eClinical^{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 double-blinded clinical trial.

Subjects, site investigators and study personnel performing any study-related assessments following study vaccine administration to the subject are blinded to vaccination and adjuvant

received. Laboratory personnel performing immunological assays will receive serum and cell specimens blinded to subject ID number and specimen visit number and allocation group. Unblinding by allocation group may occur after data lock.

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 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.

Every attempt will be made to follow all AEs, including solicited injection site and systemic reactions, unsolicited non-serious AEs, SAEs, AESIs (including Protocol Specified AESIs, MAAEs, 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

2018/2019 and 2019/2020 Fluzone Quadrivalent Influenza Vaccine (QIV)

The Sanofi Pasteur manufactured Fluzone Quadrivalent is an FDA approved vaccine indicated for active immunization in persons 6 months of age and older for the prevention of influenza disease caused by influenza viruses contained in the vaccine. Fluzone QIV is propagated in embryonated chicken eggs, chemically inactivated, disrupted and purified to yield a split virus vaccine.

2018/2019 and 2019/2020 Flublok Quadrivalent Influenza Vaccine (QIV)

The Sanofi Pasteur (Protein Sciences Corporation) manufactured FluBlok Quadrivalent is an FDA approved recombinant HA protein vaccine indicated for active immunization in persons 18 years of age and older for the prevention of influenza disease caused by influenza viruses contained in the vaccine. It contains purified HA proteins produced in a Sf9 insect cell line derived from the fall armyworm, *Spodoptera frugiperda*.

2018/2019 Fluzone and 2018/2019 Flublok Vaccine Expiry

The 2018/2019 Fluzone and Flublok are labeled to expire on June 30, 2019. The expiration date that is present on the label of licensed seasonal influenza vaccine is to ensure the product made for previous years' influenza strains are not still available for general licensed use when new seasonal vaccine becomes available against the most recent circulating strains. Historical data exists indicating that flu vaccine maintains potency for a period well beyond its expiration date. For this clinical trial, the 2018/2019 Fluzone and Flublok will be used beyond the labeled expiration date.

AF03 Adjuvant

The Sanofi Pasteur adjuvant formulation AF03 is a squalene-in-PBS emulsion stabilized by non-ionic surfactants, sorbitan oleate and macrogol cetostearyl ether prepared by the "Phase Inversion Temperature" (PIT) method.

Advax-CpG55.2 Adjuvant

The Vaxine adjuvant Advax-CpG55.2 is a combination adjuvant supplied as two separate components, Advax (delta inulin) and CpG55.2, in individual aseptic glass vials.

Advax (Delta Inulin)

Inulin is a natural storage polysaccharide of plants of the Compositae family, such as dahlias, artichoke and chicory. Inulin exists in different polymorphic forms. Advax is manufactured from highly purified inulin that is subsequently crystallized into microscopic particles of known as delta inulin and then formulated in an aqueous phosphate buffer. Advax adjuvant appears as a milky white non-viscous suspension and if left undisturbed on a stable surface for several days to weeks the delta inulin particles will slowly sediment to the bottom of the vial, leaving a clear slightly off white solution above them. The particles can be resuspended easily by simple repeated inversion of the vial several times.

CpG55.2

CpG55.2 is a completely synthetic Class B CpG oligonucleotide of 24 nucleotides in length with a full phosphorothioate backbone for increased stability. It is presented as a clear solution in an aqueous buffer.

Acquisition

2018/2019 and 2019/2020 Fluzone QIV and Flublok QIV and the AF03 adjuvant will be provided by Sanofi Pasteur.

Advax and CpG55.2 adjuvants, the individual components of Advax-CpG55.2 adjuvant will be provided by Vaxine.

Sterile Water for Injection (SWI) will be provided by DMID Clinical Materials Services Contract.

Upon request by DMID, 2018/2019 and 2019/2020 Fluzone QIV and Flublok QIV, AF03 and Advax and CpG55.2 adjuvants 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

2018/2019 and 2019/2020 Fluzone QIV and Flublok QIV, AF03 and Advax and CpG55.2 adjuvants, and SWI 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 2018/2019 and 2019/2020 Fluzone QIV and Flublok QIV, AF03 and Advax and CpG55.2 adjuvants, or SWI during this trial, contact the DMID CPM.

6.1.1 Formulation, Storage, Packaging, and Labeling

2018/2019 and 2019/2020 Fluzone QIV

Fluzone QIV is a sterile clear and slightly opalescent in color suspension of inactivated split virus for IM use. It is prepared from seasonal influenza virus candidate vaccine strains propagated in embryonated chicken eggs. The single-dose, pre-filled syringes (0.5 mL) are formulated without thimerosal or any other preservative and do not contain natural latex rubber.

2018/2019 Fluzone QIV single dose pre-filled syringes are formulated to contain 60 µg of HA per 0.5 mL dose with 15 µg of HA from each of the following four influenza virus strains recommended for the 2018/2019 influenza season: A/Michigan/45/2015 X-275 (H1N1); A/Singapore/INFIMH-16-009/2016 IVR-186 (H3N2); B/Maryland/15/2016 BX-69A(B/Colorado/06/2017-like;Victoria lineage) and B/Phuket/3073/2013 (Yamagata lineage).

The pre-filled syringes must be stored at 2°C to 8°C (36°F to 46°F). Do not freeze.

Detailed mixing instructions and necessary supplies to prepare adjuvanted 2018/2019 QIV are described in the protocol-specific MOP.

2018/2019 and 2019/2020 Flublok QIV

Flublok QIV is a sterile, clear, colorless solution of recombinant HA proteins from four influenza viruses for IM use. Vaccine may also contain residual amounts of baculovirus and Spodoptera frugiperda cell proteins, baculovirus and cellular DNA and Triton X-100. This vaccine contains no preservative (thimerosal), antibiotics or egg proteins.

2018/2019 FluBlok QIV single dose pre-filled syringes are formulated to contain 180 µg of HA per 0.5 mL dose, with 45 µg of HA derived from each of four influenza virus strains recommended for the 2018/2019: A/Michigan/45/2015 (H1N1); A/Singapore/INFIMH-16-009/2016 (H3N2); B/Maryland/15/2016 (a B/Colorado/06/2017-like virus; Victoria lineage) and B/Phuket/3073/2013 (Yamagata lineage). The pre-filled syringes must be stored protected from

light at 2°C to 8°C (36°F to 46°F). Do not freeze. Detailed mixing instructions to prepare adjuvanted 2018/2019 QIV are included in the protocol-specific MOP.

AF03

The AF03 adjuvant is a sterile injectable suspension containing 5% squalene (50 mg/mL), free from preservatives, and provided in amber glass vials containing 0.7 mL. Each 0.25 mL dose of AF03 that will be administered admixed with vaccine contains approximately 12.5 mg of squalene.

The adjuvant should be stored at a temperature ranging from +2°C to +8°C (36°F to 46°F).

Detailed mixing instructions to prepare AF03-adjuvanted 2018/2019 QIV are included in the protocol-specific MOP.

Advax-CpG55.2

Advax-CpG55.2 is a combination adjuvant formulation comprised of two components, Advax and the CpG55.2 oligonucleotide, that will be extemporaneously mixed with QIV on the day of administration in accordance with the mixing instructions detailed in the protocol-specific MOP. Each 0.5 mL dose of Advax-CpG55.2 that will be administered admixed with vaccine contains approximately 15 mg of Advax and 0.15 mg of CpG55.2.

Advax

Advax adjuvant is a sterile injectable suspension, free from preservatives, provided in 2.0 mL clear glass vials. Each 2.0 mL vial contains 0.5 mL of a 50 mg/mL suspension of delta inulin in phosphate buffered saline.

The Advax adjuvant will be stored refrigerated, protected from light at a temperature ranging from +2°C to +8°C (36°F to 46°F). Do not freeze.

CpG55.2

CpG55.2 adjuvant is a sterile injectable solution and provided in clear glass vials containing 0.5 mL of a 2 mg/ml solution of CpG55.2.

The CpG55.2 adjuvant will be stored refrigerated, protected from light at a temperature ranging from +2°C to +8°C (36°F to 46°F).

The CpG55.2 and Advax adjuvant components should be extemporaneously mixed with the appropriate investigational vaccine, and then stored at +2°C to +8°C (36°F to 46°F) until use.

Detailed mixing instructions to prepare Advax-CpG55.2-adjuvanted 2018/2019 QIV are included in the protocol-specific MOP.

Sterile Water for Injection (SWI)

- Sterile Water for Injection, USP, is sterile, nonpyrogenic, distilled water in a single dose container for intravenous administration after addition of a suitable solute. It may also be used as a dispensing container for diluent use. No antimicrobial or other substance has been added. The pH is 5.5 (5.0 to 7.0). The osmolarity is 0.
- Sterile Water for Injection (SWI) must be stored at room temperature 20°C to 25°C (68°F to 77°F) (USP Controlled Room Temperature). Avoid storing SWI in any excessive heat. For SWI, excursions between 15-30°C (59°F to 86°F) the product can continue to be used (no quarantine) but the site needs to complete the DMID Study Product Support Team Temperature Excursion Reporting Form and submit to PSTBased on UPS guidelines, excursions between 15°C and 30°C are allowed and will not be considered deviations..
- SWI will be used to prepare the Advax-CpG55.2 adjuvant prior to admixing with the 2018/2019 QIVs.

Each of the adjuvant 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 manufacturers' package inserts for the 2018/2019 and 2019/2020 (when available) Fluzone and Flublok QIVs and the manufacturers' Investigator's Brochures for both adjuvants.

Sterile empty vials (2-mL or 5-mL) will be provided with latex-free stoppers.

6.1.2 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

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 sites' research pharmacist on the same day of study vaccine.

Visually inspect the Fluzone QIV, Flublok QIV, AF03 adjuvant and the Advax-CpG55.2 adjuvant individual components, Advax and CpG55.2, and SWI upon receipt and prior to use. If the study product(s) appear(s) to have been damaged, contaminated, 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) for Fluzone QIV, Flublok QIV, AF03 adjuvant and the Advax-CpG55.2 adjuvant individual components, Advax and CpG55.2, and at 20-25°C (68°F to 77ºF, USP Controlled Room Temperature) for SWI and labeled as 'Do Not Use' (until further notice). The site PI or responsible person should immediately contact the DMID Product Support Team at 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 Fluzone QIV, Flublok QIV, AF03 adjuvant or Advax-CpG55.2 individual components, Advax and CpG55.2, and SWI are unusable, study personnel will use another vial from the study supply. Replacement vials may be requested by contacting DMID. Additional instructions for quarantine and DMID contact information are provided in the protocol-specific MOP.

For those doses that must be admixed visually inspect the Fluzone QIV or Flublok QIV plus adjuvant admixture (final mixed syringe depending on treatment arm) prior to use. The admixtures will be white cloudy suspension or milky in appearance. 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 Fluzone QIV or Flublok QIV plus adjuvant admixture 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.

Each dose of study vaccine, including those doses that must be admixed, the Fluzone QIV or Flublok QIV plus adjuvant admixture, once mixed, must be administered as soon as possible (not to exceed 30 minutes total since admixing at room temperature.

Only one dose of study vaccine should be administered. For those doses of 2018/2019 Fluzone QIV or 2018/2019 Flublok QIV that must be admixed with adjuvant gently invert the final mixed syringe 4 times immediately before the single dose of adjuvanted study vaccine is administered. **Do not shake the final mixed syringe.**

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 dose of study vaccine (volumes may vary depending on study arm) 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 admixture preparation of vaccine with adjuvant using disposable, sterile needles appropriate in length for each subject and a 1-mL disposable, sterile syringe.

6.3 Accountability Procedures for the Study Intervention/Investigational Product

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 should include, but are not limited to the following: DMID protocol number; name, dosage form, strength of the study product; capture vial numbers (optional) and pre-filled syringe number (optional) assigned sequentially by the pharmacists as vials/syringes are used (number uniquely, do not start over at 1 or repeat numbers), , manufacturer or other source; control, lot number or other identification number; expiration or retest date (memo from DMID or noted on the protocol indicating that the expiration is centrally managed is acceptable); date of receipt of the study product; quantity received from supplier; subject identification number, quantity dispenses as amount or dose per subject, balance of study product currently available, disposition of drug if not dispensed to a study subject (e.g. disposed/destroyed or retuned to supplier as per protocol or MOP or as directed by DMID), date of study vaccine preparation/administration, time of study vaccine preparation, expiration of study vaccine preparation, 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 2018/2019 and 2019/2020 Fluzone QIV and Flublok QIV, vials of AF03 and Advax-CpG55.2 (Advax and CpG55.2 individual components) adjuvants, SWI and syringe and vial 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 syringes of 2018/2019 and 2019/2020 Fluzone QIV and Flublok QIV may be destroyed in accordance with site-specific SOPs.

There are three options for documenting product accountability and dispensation:

Option 1: Retained until monitored and released for disposition

Used vials of AF03 and Advax-CpG55.2 (Advax and CpG55.2 individual components) adjuvants, SWI and vial admixtures will be retained until monitored and released for disposition, as applicable. This can occur on an ongoing basis for vials of AF03 and Advax-CpG55.2 (Advax and CpG55.2 individual components) adjuvants, SWI and vial admixtures. Used vials of AF03 and Advax-CpG55.2 (Advax and CpG55.2 individual components) adjuvants, SWI and vial 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.

Option 2: Counted and verified by two personnel before disposition

Used vials of AF03 and Advax-CpG55.2 (Advax and CpG55.2 individual components) adjuvants, SWI and vial admixtures will be retained until counted and verified by two pharmacy personnel before being released for disposition. The documentation for the verification performed by two pharmacy personnel needto be retained for sponsor's monitoring staff for review. This can occur on an ongoing basis for vials of AF03 and Advax-CpG55.2 (Advax and CpG55.2 individual components) adjuvants, SWI and vial admixtures. After the used vials of AF03 and Advax-CpG55.2 (Advax and CpG55.2 individual components) adjuvants, SWI and vial admixtures are counted and verified the vials may be destroyed in accordance with site-specific SOPs.

Option 3: Use of an Electronic Data Capture system

Used vials of AF03 and Advax-CpG55.2 (Advax and CpG55.2 individual components) adjuvants, SWI and vial admixtures can be captured in an Electronic Data Capture system which is 21 CFR Part 11 compliant. Used vials of AF03 and Advax-CpG55.2 (Advax and CpG55.2 individual components) adjuvants, SWI and vial admixtures may be destroyed on an ongoing basis in accordance with site-specific SOPs. Spornsor's monitoring staff will be provided with access to the data for verification.

Upon study completion, for all options listed above, unused syringes of 2018/2019 and 2019/2020 Fluzone QIV and Flublok QIV, unused or expired vials of AF03 and Advax-CpG55.2 (Advax and CpG55.2 individual components) adjuvants, and SWI will be retained until monitored and released for destruction.

6.4 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. Noncompliance from the dose schedule may occur. Study vaccine administration to the subject and noncompliance with the dose schedule will be recorded on the appropriate DCF.

6.5 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 Day 29 after first study vaccination or early termination, whichever occurs first. Receipt of any influenza vaccine during the 2018/2019 influenza vaccine season prior to receipt of the study vaccine (regardless of the date of receipt) will be documented. 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 28 days after the first 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 365 days after the first 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 first 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

A complete medical history will be obtained by interview of subjects at the screening visit. Subjects will be queried regarding a history of significant medical disorders of the head, eyes, ears, nose, throat, mouth, cardiovascular system, lungs, gastrointestinal tract, liver, pancreas, kidney, urologic system, nervous system, blood, lymph nodes, endocrine system, musculoskeletal system, skin, and genital/reproductive tract. A history of any allergies, cancer, immunodeficiency, psychiatric illness, substance abuse, and autoimmune disease will be solicited. At all subsequent visits 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 AESIs (including Protocol Specified AESIs, MAAEs, NOCMCs and PIMMCs).

Concomitant medications and influenza vaccination history will be collected as described in Section 6.5.

At the screening visit 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.. At the vaccination visit and at follow-up visits after each 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.

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

Reactogenicity assessments will include an assessment of solicited AEs occurring from the time of first study vaccination through Day 8, which includes an assessment of injection site reactions including pruritus, ecchymosis, erythema, induration, edema, pain, and tenderness as well as systemic reactions including fever, feverishness, fatigue, malaise, myalgia (exclusive of the

injection site), arthralgia, headache, and nausea. Pre-administration reactogenicity assessments will be performed immediately prior to first 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 the first study vaccination only (administered during visit 1). Following the first study vaccination, the vaccination site will be examined, post-administration reactogenicity assessments will be performed, and any AE/SAEs will be recorded on the appropriate DCF prior to discharge from the clinic. The study vaccination site will also be examined on approximately Day 2 and Day 8.

All subjects will complete a Memory Aid from the time of first study vaccination through Day 8. 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) at clinic study visits on approximately Day 2 and Day 8.

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: Adverse Events of Special Interest.

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 first study vaccination for all women of childbearing potential. Results must be negative and known prior to randomization on Day 1 and administration of first study vaccination to be eligible for participation in this trial and receipt of study vaccination.

The ESR evaluation will be performed locally by the site at the screening visit 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, AST, GGT, ALP, Bilirubin (total), serum lipase and serum amylase and Cr) will be collected at the screening study visit and will be sent to the Central Clinical Laboratory. The results from the clinical safety laboratory parameters collected at the screening visit must be reviewed prior to the first study vaccination and must be

within acceptable ranges to be eligible for receipt of the first study vaccination (see Section 5.1.1). The safety laboratories will be repeated prior to receipt of the first study vaccination. However, the results from the clinical safety laboratory parameters collected prior to the study vaccination will not be available or reviewed prior to the study vaccination. Clinical safety laboratory parameters collected immediately prior to the first study vaccination will serve as the baseline and will be repeated on approximately Day 8.

The volume of venous blood to be collected for ESR and clinical safety laboratory evaluations is presented in Table 3.

7.2.2 Special Assays or Procedures

Serological Assays

Serum will be collected for HAI, Neut, NAI, multiplex HA ELISA, NA ELISA and non-neutralizing Fc-effector antibody studies. Once the last subject completes the visits that occur through approximately 28 days after the first study vaccination, serum specimens collected for D1 and Day 29 visits will be shipped from the DMID CMS to Sanofi Pasteur specified research laboratories for final serological analyses. Subsequent shipments will occur once the last subject completes the visits that occur through approximately Day 118 (inclusive of D8, D57, Day 90 and Day 118), once the last subject completes the Day 180 and again once the last subject completes the Day 365 visit. Preparation of blood samples and shipping instructions for cellular immunology assays are outlined in the MOP.

Cellular Immunology Assays

This clinical trial will also investigate B cell memory responses using a multiplexed B cell FluroSpot assay evaluating IgG, IgM and IgA specific B cells. Multiparametric flow cytometry will be used to identify plasmablast/Tfh cells. PBMCs will be collected and shipped from the DMID CMS to Sanofi Pasteur specified research labs to conduct the cellular immunological assays. Preparation of blood samples and shipping instructions for cellular immunology assays are outlined in the MOP.

Transcriptomic Analyses

Whole blood transcriptomics will be done using RNA sequencing. Samples collected will be shipped from the DMID CMS to Sanofi Pasteur specified research labs to conduct transcriptomic analyses. Preparation of the blood samples and shipping instructions for transcriptomic are outlined in the MOP.

The volume of venous blood to be collected for serological, cellular immunology assays and transcriptomics is presented in Table 3.

Table 3: Venipuncture Volumes

Study Visit Number	**V00**	**V01**	**V02**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08**	**V09**	**Cumulative Blood Volume Total (mL)**
Study Day post first study vaccination	**Screening D-28 to -1**	**Enrollment Dose 1 D1**	**D2 +1**	**D8+/-1d**	**D29+/-2d**	**D57+/-3d**	**D90 +/-14 d**	**D118 +/-3 d**	**D180 +/- 14d**	**D365-14/+35d**	
Study Vaccination		X					X				
ESR	4^										**4**
Clinical Safety Laboratory Evaluations	6^	6#†		6							**18**
Serological Assays		20†		20	20	20	20†	20	20	20	**160**
Cellular Immunology Assays		80†		48	80		48†				**256**
Tempus RNA Tube		3†	3	3							**9**
Per Visit Blood Volume Total (mL)	**10**	**109**	**3**	**77**	**100**	**20**	**68**	**20**	**20**	**20**	
Running Blood Volume Total (mL)	**10**	**119**	**122**	**199**	**299**	**319**	**387**	**407**	**427**	**447**	**447**

^ 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 prior to first study vaccination. Screening WBC, Hgb, PLT, ALT, T. Bili, AST, GGT, ALP and serum lipase and serum amylase and Cr must be within the accepted ranges outlined in the inclusion criteria prior to randomization and study vaccination.

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

† Blood must be drawn immediately prior to each 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 except those done locally.

Specimens for antibody, cellular and transcriptomic assays will be shipped from the participating VTEU as outlined in the MOP.

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: Adverse Events of Special Interest.

8.1 Screening and Enrollment Visits

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

- Subjects will be provided with a description of this trial (purpose and study procedures) and asked to read and sign the ICF. The ICF will be signed prior to performing any study procedures, including administration of 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), 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 (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. Women of childbearing potential must have a negative urine or serum pregnancy test within 24 hours prior to the first study vaccination. Counsel on need for avoidance of pregnancy during the study.

- 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.

- Approximately 6 mL of venous blood will be collected for WBC, Hgb, PLT, ALT, T. Bili, AST, GGT, ALP, serum lipase and amylase and Cr for transport to the Central Clinical Laboratory. The results must be within the acceptable range as outlined in the eligibility criteria to be eligible for randomization and vaccination.

8.1.2 Visit 01, Day 1, Enrollment (Vaccination), Clinic Visit

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

- Eligibility criteria, including results from Screening of the ESR, WBC, Hgb, PLT, ALT, T. Bili, AST, GGT, ALP, serum lipase and amylase and Cr 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 study vaccination. The remaining laboratories must be within acceptable parameters as outlined in the inclusion 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 study vaccination. Any changes in medical history since the screening visit will be reviewed with subjects prior to 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 study vaccination for accuracy and completeness. Any new concomitant medications taken since the screening visit will be reviewed with subjects prior to 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 study vaccination to ensure continued eligibility. Vital signs assessed on Day 1 prior to study vaccination will be considered as baseline. Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature.

- A targeted physical examination performed prior to study vaccination, including an assessment for signs suggestive of PIMMCs, may be performed prior to 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 study vaccination for all women of childbearing potential. Results must be negative and known prior to randomization and study vaccination.

- Approximately 6 mL of venous blood will be collected immediately prior to study vaccination for baseline clinical safety labs (WBC, Hgb, PLT, ALT, T. Bili, AST, GGT, ALP, serum lipase and serum amylase and Cr) to be performed by the Central Clinical Laboratory. The results from these evaluations will not be available or reviewed prior to the study vaccination and will serve as a baseline safety assessment only.

- Approximately 20 mL of venous blood will be collected immediately prior to study vaccination for baseline serological assays.

- Approximately 80 mL of venous blood will be collected immediately prior to study vaccination for baseline cellular immunology assays.

- Approximately 3 mL of venous blood will be collected immediately prior to study vaccination for transcriptomic evaluations.

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

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

- Subjects will then receive one dose of study vaccine via a single IM injection into the deltoid muscle of the subject's 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 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.

- 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 study vaccination. If the site PI or appropriate sub-investigator deems the reaction severe enough, further instructions will be given to the subject on the proper course of action, including a return to the clinic for immediate evaluation if appropriate.

- Counsel on avoidance of pregnancy.

8.2 Follow-up Visits

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

8.2.1 Visit 02, Day 2, Clinic Visit

(Window: Day 2 +1 day post study vaccination)

- Interim medical history, including an assessment for new medical conditions, stability of chronic diseases and symptoms suggestive of AESIs (including Protocol Specified AESIs, MAAEs, NOCMCs and PIMMCs), will be obtained by interview of subjects and any changes since the previous clinic visit 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 AESIs (including Protocol Specified AESIs, MAAEs, NOCMCs and 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.
- Approximately 3 mL of venous blood will be collected for transcriptomic assays.
- Counsel on avoidance of pregnancy.

8.2.2 Visit 03, Day 8, Clinic Visit

(Window: Day 8 +/- 1 day post study vaccination)

- Interim medical history, including an assessment for new medical conditions, stability of chronic diseases and symptoms suggestive of AESIs (including Protocol Specified AESIs, MAAEs, NOCMCs and PIMMCs), will be obtained by interview of subjects and any changes since the previous clinic visit 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 AESIs (including Protocol Specified AESIs, MAAEs, NOCMCs and 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.
- Counsel on avoidance of pregnancy.
- Approximately 6mL of venous blood will be collected for clinical safety labs (WBC, Hgb, PLT, ALT, T. Bili, AST, GGT, ALP, serum lipase and amylase and Cr) to be performed by the Central Clinical Laboratory.
- Approximately 20 mL of venous blood will be collected for serological assays.
- Approximately 48 mL of venous blood will be collected for cellular immunology assays.
- Approximately 3 mL of venous blood will be collected for transcriptomic analyses.

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).

8.2.3 Visit 04, Day 29, Clinic Visit

(Window: Day 29, +/-2 days post study vaccination)

- Interim medical history, including an assessment for new medical conditions, stability of chronic diseases and symptoms suggestive of AESIs (including Protocol Specified AESIs, MAAEs, NOCMCs and PIMMCs), will be obtained by interview of subjects and any changes since the previous clinic visit 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 AESIs (including Protocol Specified AESIs, MAAEs, NOCMCs and 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.
- Counsel on avoidance of pregnancy.

- Approximately 20 mL of venous blood will be collected for serological assays.
- Approximately 80 mL of venous blood will be collected for cellular immunology assays.

8.2.4 Visit 05, Day 57, Clinic Visit

(Window: Day 57 +/- 3 days post study vaccination)

- Interim medical history, including an assessment for new medical conditions, stability of chronic diseases and symptoms suggestive of AESIs (including Protocol Specified AESIs, MAAEs, NOCMCs and PIMMCs), will be obtained by interview of subjects and any changes since the previous clinic visit will be noted.
- Receipt of any non-study influenza vaccines will be recorded on the appropriate DCF.
- SAEs, AESIs (including Protocol Specified AESIs, MAAEs, NOCMCs and PIMMCs) will be recorded on the appropriate DCF.
- A targeted physical examination, including an assessment for signs suggestive of AESIs (including Protocol Specified AESIs, MAAEs, NOCMCs and 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.
- Counsel on avoidance of pregnancy.
- Approximately 20 mL of venous blood will be for serological assays.

8.2.5 Visit 06, Day 90, Clinic Visit

(Window: Day 90 +/- 14d)

- Interim medical history, including an assessment for new medical conditions, stability of chronic diseases and symptoms suggestive of AESIs (including Protocol Specified AESIs, MAAEs, NOCMCs and PIMMCs), will be obtained by interview of subjects and any changes since the previous clinic visit will be noted.
- Receipt of any non-study influenza vaccines will be recorded on the appropriate DCF.

- SAEs, AESIs (including Protocol Specified AESIs, MAAEs, NOCMCs and PIMMCs) will be recorded on the appropriate DCF.

- A targeted physical examination performed prior to study vaccination, including an assessment for signs suggestive of AESIs (including Protocol Specified AESIs, MAAEs, NOCMCs and 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 20 mL of venous blood will be collected immediately prior to study vaccination for serological assays.

- Approximately 48 mL of venous blood will be collected immediately prior to study vaccination for immunological assays.

- Subjects will then receive one 0.5 mL dose of 2019-2020 Fluzone or Flublok QIV study vaccine via a single IM injection into the deltoid muscle of the subject's preferred arm. Subjects who received 2018-2019 Fluzone QIV will receive 2019-2020 Fluzone QIV. Subjects who received 2018-2019 Flublok QIV will receive 2019-2020 Flublok QIV. The site of injection (right or left arm) and time of study vaccine administration to the subject will be recorded on the appropriate DCF. Any SAE's will be recorded on the appropriate DCF prior to discharge.

8.2.6 Visit 07, Day 118, Clinic Visit

(Window: Day 118 +/- 3d)

- Interim medical history, including an assessment for new medical conditions, stability of chronic diseases and symptoms suggestive of AESIs (including Protocol Specified AESIs, MAAEs, NOCMCs and PIMMCs), will be obtained by interview of subjects and any changes since the previous clinic visit will be noted.

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

- SAEs, AESIs (including Protocol Specified AESIs, MAAEs, NOCMCs and PIMMCs) will be recorded on the appropriate DCF.

- A targeted physical examination, including an assessment for signs suggestive of AESIs (including Protocol Specified AESIs, MAAEs, NOCMCs and 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 20 mL of venous blood will be collected for serological assays.

8.2.7 Visit 08, Day 180, Clinic Visit

(Window: Day 180+/- 14d)

- Interim medical history, including an assessment for new medical conditions, stability of chronic diseases and symptoms suggestive of AESIs (including Protocol Specified AESIs, MAAEs, NOCMCs and PIMMCs), will be obtained by interview of subjects and any changes since the previous clinic visit will be noted.
- Receipt of any non-study influenza vaccines will be recorded on the appropriate DCF.
- Only SAEs and AESIs (including Protocol Specified AESIs, MAAEs, NOCMCs and PIMMCs), will be recorded on the appropriate DCF.
- A targeted physical examination, including an assessment for signs suggestive of AESIs (including Protocol Specified AESIs, MAAEs, NOCMCs and 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 20 mL of venous blood will be collected for serological assays.

8.3 Final Visit

8.3.1 Visit 09, Day 365, Clinic Visit

(Window: Day 365-14/+35)

- Interim medical history, including an assessment for new medical conditions, stability of chronic diseases and symptoms suggestive of AESIs (including Protocol Specified AESIs, MAAEs, NOCMCs and PIMMCs) will be obtained by interview of subjects and any changes since the previous clinic visit will be noted.
- Receipt of any non-study influenza vaccines will be recorded on the appropriate DCF.

- Only SAEs and AESIs (including Protocol Specified AESIs, MAAEs, NOCMCs and PIMMCs) will be recorded on the appropriate DCF.

- A targeted physical examination, including an assessment for signs suggestive of AESIs (including Protocol Specified AESIs, MAAEs, NOCMCs and 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 20 mL of venous blood will be collected for serological assays.

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 AESIs (including Protocol Specified AESIs, MAAEs, NOCMCs and PIMMCs), will be obtained by interview of subjects and any changes since the previous clinic visit will be noted.

- All concomitant medications will be recorded on the appropriate DCF (if prior to 28 days after the first study vaccination). Receipt of any non-study influenza vaccines will also be recorded on the appropriate DCF (if within 365 days after first study vaccination).

- All AE/SAEs will be recorded on the appropriate DCF. Unsolicited AEs (if occurs within 28 days of the first study vaccination). SAEs and AESIs (including Protocol Specified AESIs, MAAEs, NOCMCs and PIMMCs) that have occurred since the previous clinic visit will be solicited (if within 365 days after first study vaccination).

- Memory Aid information will be reviewed with subjects (if within 7 days after the first 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 AESIs (including Protocol Specified AESIs, MAAEs, NOCMCs and 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 first study vaccination).
- Post administration reactogenicity assessment will be performed (if within 7 days after the first study vaccination).
- Approximately 6 mL of venous blood will be collected for clinical safety labs (WBC, Hgb, PLT, ALT, T. Bili, AST, GGT, ALP, serum lipase and amylase and Cr) to be performed by the Central Clinical Laboratory (if within 7 days after the first study vaccination).
- Approximately 20 mL of venous blood will be collected for serological assays.
- Approximately 80 mL of venous blood will be collected for cellular immunology assays (if prior to or at the Day 90 visit).
- Approximately 3 mL of venous blood will be collected for transcriptomic assays (if prior to or at the Day 8 visit).

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 AESIs (including Protocol Specified AESIs, MAAEs, NOCMCs and 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 within 28 days after first study vaccination). Receipt of any non-study influenza vaccines will also be recorded on the appropriate DCF (if within 365 days after first study vaccination).
- All AE/SAEs will be recorded on the appropriate DCF. Unsolicited AEs (if occurs within 28 days of the first study vaccination). SAEs and AESIs (including Protocol Specified AESIs, MAAEs, NOCMCs and PIMMCs) that have occurred since the previous clinic visit will be solicited (if within 365 days after first study vaccination).

- Memory Aid information will be reviewed with subjects (if within 7 days after the first 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 AESIs (including Protocol Specified AESIs, MAAEs, NOCMCs and 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 study vaccination).

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

- Site investigators have the discretion of administering 2019/2020 Fluzone or Flublok QIV earlier than the Day 90 window (i.e. earlier than Day 76) if 10% of more of surveillance samples in the CDC geographic region surrounding the local site test positive for influenza.

- Approximately 6 mL of venous blood will be collected for clinical safety labs (WBC, Hgb, PLT, ALT, T. Bili, AST, GGT, ALP serum lipase and amylase and Cr) to be performed by the Central Clinical Laboratory (if indicated).

- Approximately 20 mL of venous blood will be collected for serological assays.

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 first study vaccination.

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

    a) Injection site reactions including pruritus, ecchymosis, erythema, induration, edema, 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 the first study vaccination through approximately 7 days after the first study vaccination. Parameters to be evaluated include WBC, Hgb, PLT, ALT, T. Bili, AST, GGT, ALP, serum lipase, serum amylase, and Cr.

4. Unsolicited AEs –non-serious AEs occurring from the time of the first study vaccination through approximately Day 29.

5. AESIs (including Protocol Specified AESIs, MAAEs, NOCMCs and PIMMCs) occurring from the time of the study vaccination through approximately 12 months after the first 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.

Adverse Events of Special Interest (AESI): An adverse event of special interest (serious or nonserious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted.

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 B: Adverse Events of Special Interest.

Protocol Specified AESIs: Dry Eye, Dry Mouth and Tearing

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 4: Injection Site Reactogenicity Grading

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

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

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

Table 5: 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 6: Subjective Systemic Reactogenicity Grading

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

* Not at injection site.

Oral temperature[#] will be graded as follows:

Table 7: 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 8: 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	141 – 155	156 – 160	>160
Hypertension (diastolic) mmHg	91 – 100	101 – 110	>110

[#] 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 9: Clinical Safety Laboratory Adverse Event Grading

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
WBC 10^3/µL (Decrease)	2.50 – 3.90	1.50 – 2.49	<1.50
WBC 10^3/µL (Increase)	10.60 – 15.00	15.01 – 20.00	>20.00

Hgb g/dL (Decrease) (Female)	10.1 – 11.4	8.5 – 10	<8.5
Hgb g/dL (Decrease) (Male)	11.0 – 12.4	9.5 – 10.9	<9.5
Platelets 10^3/µL (Decrease) EDTA	125 – 139	100 – 124	<100
Platelets 10^3/µL (Increase) EDTA	416 – 550	551– 750	>750
Platelets K/cu mm (Decrease) Citrate	115-124	100-114	<100
Platelets K/cu mm (Increase) Citrate	376-550	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
Aspartate Amino Transferase IU/L (Increase) (Female)	37-90	91-180	> 180
Aspartate Amino Transferase IU/L (Increase) (Male)	44-108	109-215	> 215
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
Gamma-Glutamyl Transferase IU/L (Increase) (Female)	33-80	81-160	> 160
Gamma-Glutamyl Transferase IU/L (Increase) (Male)	50-123	124-245	> 245
Alkaline Phosphatase IU/L (Increase) (Female)	116-230	231-345	> 345
Alkaline Phosphatase IU/L (Increase) (Male)	116-230	231-345	> 345
Serum Amylase	122-182	183-242	>243
Serum Lipase	61-90	91-180	> 181
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 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 the first study vaccination through 7 days after the first study vaccination.

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

Unsolicited non-serious AEs will be documented and reported from the time of the first study vaccination through approximately Day29.

SAEs and AESIs (including Protocol Specified AESIs, MAAEs, NOCMCs and PIMMCs) will be documented and reported from the time of the first study vaccination through approximately 12 months after the first 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 Advantage eClinical[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

Upon awareness, pregnancies occurring in subjects will be recorded on the Pregnancy Report DCF. All pregnancies reported during the course of this trial will be followed to pregnancy outcome. With the subject's permission, a venous blood sample(s) for serological assays will be collected per protocol though large volume blood samples for cellular immunological assays will be discontinued. Subjects who become pregnant will not be excluded from receiving the seasonal flu vaccine at Day 90, unless there are contraindications. Subjects will be followed for safety as per the protocol.

Pregnant subjects will be contacted at least once every 12-16 weeks during pregnancy, following delivery, and at approximately one month following birth (if live birth) or one to two months following still birth.

Subjects who become pregnant will be approached regarding their interest to enroll in the Sanofi Pregnancy Registry. This Registry program is not a part of this research study. Participation is completely voluntary. If subjects choose to enroll they can contact Sanofi via email at USPVmailbox@sanofi.com or call Customer Service at 1-800-633-1610 option#2 to discuss enrollment in the Pregnancy Registry for Influenza.

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 first study vaccination through approximately 28 days after the first study vaccination.

SAEs and AESIs (including Protocol Specified AESIs, MAAEs, 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 first 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

Enrollment will start with 6 sentinel subjects, one each from each study group (groups 1-6). Subjects will be followed through Day 8. If any of the pre-specified events outlined in Section 9.5.1 occur, the study will be halted and reviewed by the DSMB. If no prespecified events occur, randomization and vaccination can proceed. All 6 subjects will then be followed according to protocol.

It is anticipated that both adjuvant formulations (AF03 and Advax-CpG55.2) will be available at the start of study enrollment. However, if the Advax or CpG55.2 components for Advax-CpG55.2 are not available, the study will proceed only with groups 1, 2, 4 and 5 open for enrollment for the remaining subjects (up to 240) in groups 1, 2, 4 and 5. For the sentinel subjects, one subject from groups 1, 2, 4 and 5 will be enrolled and followed through Day 8. If any of the pre-specified halting rules occur, the study will be halted and reviewed by the DSMB. If no pre-specified events occur, randomization will proceed in groups 1, 2, 4 and 5 and enrollment will continue for the remaining subjects in groups 1, 2, 4 and 5.

9.5.1 Halting Rules for the Sentinel Subjects

- Any subject experiences ulceration, abscess or necrosis at the injection site.
- Any subject experiences laryngospasm, bronchospasm or anaphylaxis within 24 hours after administration.
- Any subject experiences generalized urticaria (defined as occurring at more than two body parts) within 72 hours after administration of study product.
- Any subject experiences an SAE (except for accident or trauma) after administration of the 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 that experiences grade 3 AE including lab, local or systemic solicited reactogenicity events (excluding measured grades of erythema and induration alone)

- Two or more subjects experience the same grade 2 (same HLGT by MedDRA coding) AE including local or systemic solicited reactogenicity events (excluding measured grades of erythema and induration alone)

9.5.2 Halting for Study

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 after the first study vaccination:

- Any subject experiences ulceration, abscess or necrosis at the injection site that is considered related to study product administration.
- Any subject experience laryngospasm, bronchospasm or anaphylaxis within 24 hours after administration of study product that is considered related to study product.
- Two or more subjects experience generalized urticaria (defined as occurring at more than two body parts) within 72 hours 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.
- 10% of subjects (minimum 3 subjects) experience a grade 3 injection site or systemic solicited adverse event (excluding measured grades of erythema and induration alone).
- 10% of subjects (minimum 3 subjects) experience same grade 3 AE (unsolicited and laboratory abnormality), in the same HLGT by MedDRA coding, considered related to study product.

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 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.
Data and Safety Monitoring Board (DSMB)

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, AESIs (including Protocol Specified AESIs, MAAEs, NOCMCs and PIMMCs) and HAI and Neut antibody assay results. The DSMB will review SAEs on a regular basis and ad hoc during this trial. The DMID Medical Monitor and the ISM (as deemed necessary) will be responsible for reviewing SAEs in real time.

The DSMB will review the data when the 8-day reactogenicity and clinical safety laboratory data following the first study vaccination is available for 50% of study subjects. Enrollment will not be paused for this review.
The DSMB will conduct the following reviews:

- An Organizational Meeting that occurs prior to subject enrollment

- Scheduled Data Review Meeting when 50% of the subjects reach Day 8 post first injection and all clinical safety laboratory data following the first study vaccination are available.

- Scheduled Data Review Meeting when an expedited report containing safety and immunogenicity analyses for HAI, NAI and Neut antibody assays unblinded by group has been created by the SDCC after the interim clinical database is cleaned, monitored and locked and all HAI, NAI, and Neut data for Day 1 and Day 29 and safety date through Day 57 after the first study vaccination have been received. If other immunological analyses are available, these data may be reviewed at this meeting.

- 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 conducted: 6 to 8 months after clinical database lock to review the cumulative unblinded safety and immunogenicity data for this trial. If a final meeting is held, the data may be provided in a standard summary format, or provided as

the CSR. 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 study is to assess, in healthy adults ages 18-45, the safety, reactogenicity and immunogenicity of either the 2018/2019 seasonal Fluzone or Flublok QIV manufactured by Sanofi Pasteur administered intramuscularly given without adjuvant or with one of two adjuvants, AF03 or Advax-CpG55.2. These study arms are included to allow evaluation of the potential of each of the two adjuvants to enhance the immune response to either the 2018/2019 seasonal Fluzone QIV or the 2018/2019 seasonal Flublok QIV.

11.2 Study Hypotheses

This Phase I 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 either the 2018/2019 seasonal Fluzone or Flublok QIV administered without adjuvant or with AF03 or Advax-CpG55.2 adjuvants, 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 Table 1.

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, 18-45 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 a previous DMID trial (DMID 15-0064, NCT02624219), 4 VTEUs recruited 275 healthy subjects, 19 to 64 years of age, in 20 weeks. In this trial, approximately 3% of subjects, 19 to 64 years of age, were excluded from the per protocol (PP) analysis for the Day 22 primary immunogenicity outcome either because they were lost-to-follow-up or because they had a protocol deviation requiring their exclusion from the PP analysis. The rate of per protocol exclusions for the Day 29 visit in this protocol is expected to follow a similar trend.

A total of 40 subjects will be enrolled and randomized in each group. Assuming up to 3% drop out by Day 29, it is expected that at least 38 subjects per group will be available for the primary immunogenicity analysis. If Advax-CpG55.2 is not available, the study will proceed only with groups 1, 2, 4 and 5 open for enrollment for the remaining subjects (up to 240 or 60 per group) in groups 1, 2, 4 and 5. In this case, assuming the same dropout rate of 3%, it expected that at least 58 subjects per group will be available for the primary immunogenicity analysis.

Follow-up will consist of 2 segments. The first encompasses the core data for this trial and will consist of results for all study visits through approximately 28 days after study vaccination. The second segment consists of a 6-month immunogenicity assessment and follow-up safety assessments through approximately 12 months after study vaccination.

11.4.3 Sample Size

This study is planned to enroll 40 subjects per group. If Advax-CpG55.2 is not available, the study will proceed only with groups 1, 2, 4 and 5 open for enrollment for the remaining subjects (up to 240 or 60 per group) in groups 1, 2, 4 and 5. This study is not designed to test a formal null hypothesis. Rather, it is intended to obtain sufficient data to obtain meaningful estimates of the immune response and to uncover any safety issues that occur at a sufficiently high rate that they might be observed in a study of this size. For the purposes of summarizing we will assume a type one error rate, alpha = 0.05, and will not adjust for multiple comparisons. The following tables illustrate the precision and power for select estimates and comparisons of interest. Table 10 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 sentinel subjects (N=4 or 6), for a single adjuvanted/ unadjuvanted treatment arm/stratum (N = 40 or 60), for all subjects receiving the same seasonal QIV (N= 120), for all subjects in the trial (N=240).

Table 10: Probability (%) to Detect Safety Events

Event Frequency	N = 4	N = 6	N = 40	N = 60	N = 120	N = 240
≥10% Very Common	34	46	98	>99	>99	>99
≥1% Common	3	5	33	45	70	91
≥0.1% Uncommon	<1	<1	3	5	11	21
≥0.01% Rare	<1	<1	<1	<1	1	2

Binomial confidence intervals (CI) are widest (have the least precision) when the response rate is 50%. Table 11 is presented to indicate the worst-case scenario for precision of observed exact (Clopper-Pearson) binomial confidence intervals.

Table 11: Precision of Binomial Confidence Intervals

N	95% CI
4	6-94
6	11-89
40	33 -67
60	36-64
120	40-60
240	43-57

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

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

Table 12 illustrates the minimum detectable differences in the proportion of subjects responding (e.g., attaining seroconversion or a titer ≥1:40) between two adjuvanted treatment arms using a two-sided Likelihood Ratio Test and alpha = 0.05. It is assumed that approximately 3% of the

subjects (N=2) in each treatment arm will be excluded from the per protocol analysis of primary immunogenicity endpoints leaving N=38 subjects per treatment arm. If Advax-CpG55.2 is unavailable, approximately 3% of the subjects (N=2) in each treatment arm will be excluded from the per protocol analysis of primary immunogenicity endpoints leaving N=58 subjects per treatment arm. Seroconversion rates of 40% to 90% are considered.

Table 12: Minimum Detectable Difference in Proportion Responders with 80% Power

Assumed Proportion of subjects with titer ≥ 40 in comparator arm (p_c)	Minimum detectable difference in response rate (p_c-p_e), N=38 per group	Minimum detectable difference in response rate (p_c-p_e), N=58 per group
0.40	0.32	0.26
0.50	0.30	0.25
0.60	0.28	0.23
0.70	0.24	0.20
0.80	0.18	0.16
0.90	0.10	0.10

11.5 Planned Interim Analyses

Interim analyses will only be used to terminate this trial in the event that unanticipated safety events deemed to be of sufficient concern require such action by the sponsor. These assessments will not be made on the basis of testing a formal statistical hypothesis; therefore, p-value adjustment will not be made to any analyses. A DSMB will be convened by DMID to review study progress and participant, clinical, safety, reactogenicity and immunogenicity data as described in Section 9.6.2.

Clinical, safety, and reactogenicity data through approximately 56 days after study vaccination will represent the interim clinical database for this trial. Once the last subject completes the visit that occurs approximately 56 days after first study vaccination, the interim clinical database will be cleaned, monitored and locked. Upon receipt of immunogenicity data for Day 1 and Day 29 (HAI, NAI, and Neut data) and safety data through Day 57, the sponsor will authorize the DCC to transfer to Sanofi Pasteur a copy of this unblinded data set. An expedited report containing analyses of safety data through Day 57 and HAI, NAI, and Neut data from baseline (Day 1) and Day 29 unblinded by treatment group only will be prepared by the SDCC. These analyses may be made available to the sponsor and pharmaceutical partners for planning subsequent trials as

well as the DSMB for review. Other immunological analyses that are available may also be included in the expedited report and may also be reviewed by the DSMB.

The analyses performed for the expedited report or using the data set provided to Sanofi Pasteur will not be used to make any decisions concerning the conduct of this trial. As it is anticipated that subjects will remain in long term safety follow-up at the time of these analyses, blinded investigators and DMID medical monitors not involved in the analysis, publication, or clinical study report preparation will be responsible for assessing SAEs and AESIs (including Protocol Specified AESIs, MAAEs, NOCMCs and PIMMCs) until all subjects have completed the final follow-up visit.

11.5.1 Interim Safety Review

An interim safety review may include enrollment and demographic information, medical history, concomitant medications, physical assessments, clinical laboratory values, dosing compliance, and solicited and unsolicited AE/SAEs. Additional data may be requested by the DSMB, and interim statistical reports may be generated as deemed necessary and appropriate by DMID. The DSMB may receive data in aggregate and presented by treatment arm, including expected and observed rates of the expected AEs. The DSMB will review grouped data in the closed session only. The DSMB will meet and review these data at scheduled time points or ad hoc as needed during this trial as defined in the DSMB charter. As an outcome of each review/meeting, the DSMB will make a recommendation as to the advisability of proceeding with study vaccinations (as applicable), and to continue, modify, or terminate this trial.

Additionally, this trial will be monitored to determine if any of the halting rules described in Section 9.5 are met.

11.6 Final Analysis Plan

Subject unblinding will occur and the final CSR will be completed after the last subject's last visit is completed, the final clinical database including all long-term safety follow-up data is cleaned, monitored and locked, and all primary and secondary immunogenicity data are available. After such data are reported in the database and the data are considered clean and complete, a "topline" subset of the immunogenicity tables planned for the CSR will be provided to DMID and Sanofi Pasteur. Additional exploratory immunogenicity endpoint data not available at the time of CSR preparation may be included in an addendum to the CSR, manuscript(s), or other report.

A formal statistical analysis plan which defines the analyses to be included in the expedited report and the final CSR will be developed, finalized, and submitted to the FDA, prior to unblinding for any analysis.

11.6.1 Analysis Populations

The Safety Analysis population includes all subjects who received the first dose of study vaccine.

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

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

- Data from all available visits for subjects found to be ineligible at baseline.
- Data from all visits for subjects that did not contribute venous blood samples for immunogenicity testing (HAI, NAI or Neut antibody assays) at baseline (Day 1).
- Data from all visits subsequent to major protocol deviations, such as:
    - Receipt of non-study licensed live vaccine within 30 days before or after the first study vaccination,
    - Receipt of non-study licensed inactivated vaccine within 14 days before or after the first study vaccination,
    - Receipt of immunosuppressive therapy (e.g., corticosteroids) within 30 days before or after the first 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 after the first study vaccination (1-7 days post study vaccination) and as the maximum severity over all 8 days. Additionally, solicited AEs will be analyzed by taking the most severe response over the follow-up period, dichotomizing into a binary variable (none versus mild, moderate, or severe) and using standard techniques, such as exact confidence intervals, to summarize the proportion of subjects reporting each symptom, any injection site symptom, and any systemic symptom. Summaries of solicited AEs will be presented for the first study vaccination by treatment arm. The proportion of subjects reporting symptoms may be compared between treatment arms using Chi-square or Fisher's exact 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 AESIs (including Protocol Specified AESIs, MAAEs, NOCMCs and PIMMCs) are likely to be small in this trial and will be reported by detailed listings showing the event description, MedDRA® preferred term and SOC, relevant dates (study vaccinations and AEs), severity, relatedness, and outcome for each event. Non-serious unsolicited AEs will be summarized as number and percentage of subjects reporting at least one event in each MedDRA® preferred term and SOC, cross tabulated by severity and relationship to study product. Additionally, the proportion of subjects and exact 95% confidence intervals of AEs in aggregate and by MedDRA® categories will be computed. 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 Humoral Immunogenicity Data

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

Immune responses in terms of strain-specific HAI, NAI, and Neut antibody titers will be summarized by treatment arm at each time point. Analyses will include GMTs, ratio of GMTs between adjuvanted and unadjuvanted study arms, percentage of subjects achieving seroconversion (as defined in Table 1) and percentage of subjects with a titer ≥1:40 (HAI and Neut only) along with corresponding 95% confidence intervals. Descriptive summary statistics will be provided for all assays and time points. These immune responses against vaccine strains will also be presented by serostatus and previous influenza vaccination. The correlation between

HAI, NAI and Neut antibody titers will be evaluated. Plots such as reverse cumulative distributions or longitudinal presentations of GMTs will be presented.

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

11.6.4 Exploratory Cellular Immunogenicity Data

Summaries of exploratory cellular immunology assays will be presented for the Per Protocol Population and will be presented overall as well as by treatment arm.

Analysis of the exploratory cellular immunogenicity data will be primarily descriptive. Association of exploratory endpoints with HAI, NAI, and Neut antibody titers will be assessed.

11.6.5 Exploratory Transcriptomics Data

For the transcriptomics exploratory analysis, RNA-Seq data will be pre-processed by removing adapters and low-quality reads and mapping sequences to the latest human reference genome using splice-aware alignment software such as *HISAT2*[52]. Gene expression quantification will be carried out by using the *Subread* software [53] using the latest Ensembl [54] gene model annotations as a reference. Systematic differences in sequence coverage between samples will be accounted for using the TMM normalization method [55] as implemented in the *edgeR* R package [56]. Principal component analysis, non-metric multidimensional scaling, and hierarchical clustering analysis will be used to identify potential outliers and systematic batch effects. Negative binomial models as implemented in *edgeR* [56] will be used to identify genes for each study group and post-vaccination day (Day 2 and 8) that were differentially expressed (DE) compared to pre-vaccination. If the analysis reveals a systematic batch effect that is not associated with study group or study visit, it will be accounted for by adding a batch blocking factor as part of the negative binomial models. To control for testing multiple genes, the false-discovery rate (FDR) based on the Benjamini-Hochberg procedure [57] as implemented in the *p.adjust* R function will be applied. The *pvclust* R package [58] will be used to identify co-expressed DE gene clusters. Mean cluster $\log_2$ fold change time trends and associated 95% bootstrap CIs will be presented by group across post-vaccination days. To functionally characterize DE genes, pathway enrichment analysis based on the latest MSigDB [59] and KEGG [60] databases as well as Blood Transcription Modules [61] will be carried out using the implementation provided by the *goseq* R package [62] which accounts for gene length bias. Pathway maps color-coded by treatment effect ($\log_2$ fold change compared to pre-vaccination)

will be visualized for significantly enriched KEGG pathways. Pathway enrichment trends by group across post-vaccination days will be visualized using heatmaps and time trend plots of median pathway responses (based on median average $\log_2$ fold changes of all pathway members) and associated 95% bootstrap CIs. Regularized linear regression analysis as implemented in the glmnet R package [63] will be utilized to identify gene expression changes that are predictive of later adaptive humoral immune response. Cross-validation will be used to select optimal models.

11.6.6 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 Federal Wide 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. IRB approved recruitment process, screening script, and materials for subjects may be utilized. 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. During recruitment, potential subjects may be screened for eligibility by phone or email before obtaining written consent, per an IRB-approved process that ensures confidentiality. At the first clinic visit 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. The subject will be asked to consent specifically to genetic testing (transcriptomics) planned for this study.

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.

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

This trial will be inclusive of all subjects, 18 to 45 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. Should the outcome of this trial be deemed acceptable, additional trials may be initiated including those in other populations.

It is unknown if Fluzone QIV or Flublok QIV with AF03 or Advax-CpG55.2 adjuvant pose any risks to an unborn child. However, the unadjuvanted QIVs are recommended for pregnant

women and have not shown safety signals. Women of childbearing potential must utilize a highly effective method of contraception that is defined as one that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly (effective methods of birth control are outlined in the inclusion criteria, section 5.1.1). 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 the first study vaccination. Female subjects who become pregnant while participating in this trial will be provided information to enroll in the Sanofi Pregnancy Registry, if they so choose. This registry program is not a part of this research study and participation in the registry program is completely voluntary.

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 written consent of the subject and approval by 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 vaccines 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.

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 for transcriptomic profiling assessments, a form of genetic testing. Subjects will be asked to give explicit consent to participate in the per protocol defined transcriptomics study.

Subjects will be asked to consent to the future research use of excess/residual specimens and the sharing of genetic information and samples. If they choose to not provide permission for excess blood and future use, they will not be eligible for randomization and enrollment into the study. To maintain statistical power in follow-on analyses it is important that excess/residual blood collection be included in as many subjects as possible, due to the limited sample size per treatment arm.

The amount of venous blood collected for serological and cellular immunology assays exceeds the amount of blood required to perform per protocol (PP) defined immunologic assays by approximately 175 mL collected across the study. This excess/residual blood and corresponding serum, plasma and PBMCs will be used as back-up specimens for PP defined assays or designated for future research use and stored indefinitely at a central storage facility. Collection of excess/residual samples during the course of the study will help facilitate rapid follow-on analyses, if warranted, to provide more comprehensive scientific insights into the impact (safety and immunological) of two novel adjuvants on the host response to vaccination.

To maintain statistical power in follow-on analyses it is important that excess/residual blood collection be included in as many subjects as possible, due to the limited sample size per treatment arm. Samples designated for future research use may be used for additional immunological assessments that may include but are not limited to antibody epitope mapping, B and T cell repertoire determination, non-traditional immune assay development, determination of innate immune factors and the ability of vaccine-induced antibodies to cross-react to different

influenza proteins and virus strains. These blood samples 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. Future use DNA testing may also be warranted to understand genetic factors involved in vaccination failures, despite the presence of a specific adjuvant.

Future research use specimens, upon written request and approval from DMID, may be shared with investigators at the participating VTEU sites, with other investigators or company designated research laboratories for purposes of conducting additional immunological assessments other than PP analysis. DMID would authorize shipment from the DMID CAR. There are no benefits to subjects in the collection, storage and future research use of their samples/specimens. Risks for excess blood drawn may include anemia, however the risk is low since the total amount drawn for this study and future use does not exceed a unit of blood.

Future research use samples/specimens 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.

Subjects may withdraw permission to use samples for future use at any time. They will need to contact the study site and the samples will be removed from the study repository after this study is completed and documentation will be completed that outlines the reason for withdrawal of permission for future use of samples. Subjects who withdraw consent before the last visit will not have the excess blood drawn for future use.

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 56 days after the first study vaccination will represent the interim clinical database for this trial. Once the last subject completes the visit that occurs approximately 56 days after the first study vaccination, the primary clinical database will be cleaned, monitored and locked. Upon receipt of immunogenicity data for Day 1 and Day 29 (HAI, NAI, and Neut data) and safety data through Day 57, the sponsor will authorize the DCC to transfer to Sanofi Pasteur a copy of this unblinded data set.

An expedited report containing immunogenicity analyses for HAI, NAI, and Neut antibody assays unblinded by treatment group only will be created by the SDCC after the interim clinical database is cleaned, monitored and locked and all HAI, NAI, and Neut data for Day 1 and Day 29 after the first study vaccination have been received. Other immunological analyses that are available may also be included in the expedited report. These analyses may be made available to the sponsor and pharmaceutical partners for planning subsequent trials and the DSMB for review.

The analyses performed for the expedited report or the data set provided to Sanofi Pasteur will not be used to make any decisions concerning the conduct of this trial. As it is anticipated that subjects will remain in long term safety follow-up at the time of these analyses, blinded investigators and DMID medical monitors not involved in the analysis, publication, or clinical study report preparation will be responsible for assessing SAEs, AESIs (including Protocol Specified AESIs, MAAEs, NOCMCs and PIMMCs) until all subjects have completed the final follow-up visit. All analyses of data included in the expedited report for early release will be included in the final clinical study report (CSR).

The final CSR will be completed after the last subject's last visit is completed, the final clinical database including all long-term safety follow-up data is cleaned, monitored and locked, and all primary and secondary immunogenicity data are available. After such data are reported in the

database and the data are considered clean and complete, a "topline" subset of the immunogenicity tables planned for the CSR will be provided to DMID and Sanofi Pasteur. Additional exploratory immunogenicity endpoint data not available at the time of CSR preparation may be included in an addendum to the CSR, manuscript(s), or other report.

A formal statistical analysis plan will be developed, finalized, and submitted to the FDA, prior to unblinding for any analysis, which defines the analyses to be included in the expedited report and the final 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 Advantage eClinical[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

17 LITERATURE REFERENCES

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18 APPENDICES

Appendix A: Schedule of Study Procedures and Evaluations

Appendix B: Adverse Events of Special Interest

APPENDIX A. SCHEDULE OF STUDY PROCEDURES AND EVALUATIONS

Table 13: Schedule of Study Procedures and Evaluations

Study Visit Number	**V00**	**V01**	**V02**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08**	**V09**	**Early Termination**	**Unscheduled**
Screening, Enrollment/Study Day and post first study vaccination	**Screening D-28 to -1**	**Enrollment D1**	**D2+1d**	**D8+/-1d**	**D29+/-2d**	**D57+/-3d**	**D90+/-14d**	**Day118+/-3d**	**D180 +/-14d**	**D365 -14/+35**		
Informed Consent[∞]	X[∞]											
Demographic Information	X											
Eligibility Criteria	X	X[†¬1]										
Medical History[@]	X	X[†¬]	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X[†¬]	X	X	X						X[6]	X[6]
Vital Signs (Oral Temperature[%], Pulse and BP)	X	X[$]									X	X
Height and Weight	X											
Physical Examination	X[2]	{X}	{X}	{X}	{X}	{X}	{X}[†]	{X}	{X}	{X}	{X}	{X}
Urine or Serum Pregnancy Test	X[^]	X[†^]										
Venous Blood Collection for Screening Laboratories	X[≠]											
Enrollment in Advantage eClinical[SM] and Randomization		X[†]										
Venous Blood Collection for Clinical Safety Laboratory Evaluations~		X[†,~]		X[~]							X[7]	X
Venous Blood Collection for Serological Assays		X[†]		X	X	X	X[†]	X	X	X	X	X
Venous Blood Collection for Cellular Immunology Assays		X[†]		X	X		X[†]				X[8]	
Venous Blood Collection for Transcriptomics		X[†]	X	X							X[9]	
Pre-Administration Reactogenicity Assessments		X[†]										

Study Visit Number	**V00**	**V01**	**V02**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08**	**V09**	**Early Termination**	**Unscheduled**
Screening, Enrollment/Study Day and post first study vaccination	**Screening D-28 to -1**	**Enrollment D1**	**D2+1d**	**D8+/-1d**	**D29+/-2d**	**D57+/-3d**	**D90+/-14d**	**Day118+/-3d**	**D180 +/-14d**	**D365 -14/+35**		
Study Vaccination		X					X*					
20-minute Evaluation After Study Vaccination		X										
Examine Study Vaccination Site		X	X	X							X[7]	X[7]
Post-Administration Reactogenicity Assessments		X									X[7]	X[7]
Distribute Memory Aid and Study-Related Materials		X										
Review Memory Aid			X	X							X[7]	X[7]
AE/SAE Assessment		X[&,3]	X[&,3]	X[&,3]	X[3]	X	X[4]	X[4]	X[4]	X[4]	X[3,6]	X[3,6]

∞ Prior to study procedures.
¬ Review/confirm information or activity in subjects previously consented and screened.
† Prior to study vaccination.
1 Review results of ESR and clinical safety laboratory evaluations.
@ Complete medical history (including solicitation for receipt of any non-study influenza vaccine) will be obtained by interview of subjects at the screening visit and interim medical history will be obtained by interview of subjects on Day 1 prior to study vaccination and at follow-up visits after study vaccination.
$ Vital signs assessed on Day 1 prior to the study vaccination will be considered as baseline.
% Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature.
2 At the screening visit a physical examination will be performed on all subjects to include the following organs and organ systems: skin, head and neck, lungs, heart, liver, spleen, extremities, lymph nodes, and nervous system.
{} Targeted physical examination if indicated based on review of interim medical history.
^ Performed locally by the site at the screening visit (optional); Must be performed within 24 hours prior to study vaccination for all women of childbearing potential. Results must be negative and known prior to randomization on Day 1 and administration of study vaccination.
≠ ESR Performed by local laboratory, WBC, Hgb, PLT, ALT, T. Bili, AST, GGT, ALP, serum lipase, serum amylase and Cr will be sent to the central clinical laboratory.
~ Includes, WBC, Hgb, PLT, ALT, T. Bili, AST, GGT, ALP, serum lipase, serum amylase and Cr.
& Inclusive of reactogenicity assessments performed on the day of study vaccination through 7 days after study vaccination.
[3] AEs (if visit occurs on or before Day 29), SAEs, AESIs (including Protocol Specified AESIs, MAAEs, NOCMCs and PIMMCs), for subjects who are being followed for safety.
[4] SAEs and AESIs (including Protocol Specified AESIs, MAAEs, NOCMCs and PIMMCs), for subjects who are being followed for safety.

[5] Investigators have the discretion of administering 2019/2020 Fluzone or Flublok earlier than the Day 90 window (i.e earlier than Day 76) if 10% of more of surveillance samples in the CDC geographic region surrounding the local site test positive for influenza.

[6]If within 365 after first study vaccination

[7] If within the first 7 days after the first study vaccination

[8] If prior to or at the D90 visit

[9] If prior to or at the D8 visit

* Seasonal QIV 2019/2020

APPENDIX B. ADVERSE EVENTS OF SPECIAL INTEREST

MAAEs

NOCMCs

PIMMCs:

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 parotitis
- Autoimmune thrombocytopenia
- Good pasture syndrome
- Idiopathic pulmonary fibrosis
- Pernicious anemia
- Raynaud's phenomenon
- Sarcoidosis
- Sjögren's syndrome
- Stevens-Johnson syndrome
- Uveitis

Protocol Specified AESIs

- Dry Eyes
- Tearing
- Dry Mouth