BP-I-23-001

RANDOMIZED, DOUBLE-BLIND, PHASE 2 STUDY TO ASSESS SAFETY AND IMMUNOGENICITY OF A/H5 INACTIVATED MONOVALENT INFLUENZA VACCINES AT DIFFERENT ANTIGEN DOSE LEVELS ADJUVANTED WITH AS03® OR MF59®

IND Sponsor: Biomedical Advanced Research and Development Authority (BARDA)
[redacted]

Version of Protocol: 3.0

Date of Protocol: 05 August 2024

CONFIDENTIAL

All financial and nonfinancial support for this study will be provided by BARDA. The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without the expressed, written consent of BARDA.

PROTOCOL APPROVAL - SPONSOR SIGNATORY

Study Title	Randomized, Double-Blind, Phase 2 Study to Assess Safety and Immunogenicity of A/H5 Inactivated Monovalent Influenza Vaccines at Different Antigen Dose Levels Adjuvanted with AS03® or MF59®
Protocol Number	BP-I-23-001
Protocol Version	V3.0
Protocol Date	05 August 2024

Protocol reviewed by:

[redacted]

Protocol accepted and approved by:

[redacted]

Signature

Date

STATEMENT OF COMPLIANCE

Each institution engaged in this research will hold a current Federalwide Assurance (FWA) issued by the Office of Human Research Protection (OHRP) for federally funded research. The Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) must be registered with OHRP as applicable to the research.

The study will be carried out in accordance with the following as applicable:

- United States Code of Federal Regulations (CFR) 45 CFR Part 46: Protection of Human Subjects
- Food and Drug Administration (FDA) Regulations: 21 CFR Part 50 (Protection of Human Subjects), 21 CFR Part 54 (Financial Disclosure by Clinical Investigators), 21 CFR Part 56 (Institutional Review Boards), 21 CFR Part 11 (Electronic Records; Electronic Signatures), and 21 CFR Part 312 (Investigational New Drug Application), and/or 21 CFR 812 (Investigational Device Exemptions)
- The International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6(R2) Good Clinical Practice (GCP), and the 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
- Any additional Federal, State, and Local Regulations and Guidance

The signature below provides the necessary assurance that this study will be conducted according to all stipulations of the protocol including statements regarding confidentiality, and according to local legal and regulatory requirements, US federal regulations, and ICH E6(R2) GCP guidelines.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

2. SYNOPSIS

Name of Sponsor/Company: Biomedical Advanced Research and Development Authority (BARDA)

Names of Investigational Products:

Influenza vaccine antigens:

- Egg-A/Astrakhan/3212/2020 (H5N8) (Sanofi Pasteur Inc.)
- Egg-A/bar-headed goose/Qinghai Lake/1A/2005 (H5N1) (Sanofi Pasteur Inc.)

Adjuvants:

- AS03A (GSK)
- MF59 (CSL Seqirus)

Names of Active Ingredients:

Antigens: Sanofi egg-based vaccine antigens derived from A/Astrakhan/3212/2020 (H5N8) and A/bar-headed goose/Qinghai Lake/1A/2005 (H5N1) influenza virus strains

Adjuvants: AS03A full dose, AS03A half dose, and MF59

Title of Study: Randomized, Double-blind, Phase 2 Study to Assess Safety and Immunogenicity of A/H5 Inactivated Monovalent Influenza Vaccines at Different Antigen Dose Levels Adjuvanted with AS03® or MF59®

Protocol Number: BP-I-23-001

Version Number: 2.0

Study center(s): Approximately 15-20 clinical sites in the United States (US)

Study period (years):	**Phase of Trial:** 2
Estimated date first participant enrolled: August 2024 Estimated date last participant completed: May 2025	

Study Objectives:

Primary Objectives

Safety

- To assess the safety and reactogenicity for 8 days following each vaccination, inclusive of the vaccination day (Day 1 through Day 8 and Day 22 through Day 29) of different antigens and antigen doses of vaccine given with AS03A full dose, AS03A half dose, or MF59 adjuvant administered intramuscularly (IM) on Days 1 and 22, as determined by solicited local and systemic reactogenicity symptoms.

Immunogenicity

- To assess the serum hemagglutination-inhibition (HAI) antibody seroprotection rate on Day 43, following IM administration of the study vaccines on Days 1 and 22.

Secondary Objectives

Safety

- To assess the occurrence of any unsolicited treatment-emergent adverse events (TEAEs) within 22 days following each vaccination, inclusive of the vaccination day (Day 1 through Day 22 and Day 22 through Day 43) for the study vaccines.
- To assess the occurrence of treatment-emergent serious adverse events (SAEs) and medically attended adverse events (MAAEs), including a subset of specific potentially immune-mediated diseases (pIMDs), for the study vaccines through Day 203.

Immunogenicity

- To assess the serum HAI antibody titers, seroprotection rates, and seroconversion rates elicited by the study vaccines through Day 203.
- To assess the serum microneutralization (MN) antibody titers and seroconversion rates elicited by the study vaccines through Day 203.

Methodology:

This is a randomized, double-blind, phase 2 study to assess safety and immunogenicity of egg-based H5N8 and H5N1 influenza vaccines at different antigen dose levels (3.75, 7.5, and 15 μg) adjuvanted with AS03A full dose, AS03A half dose (H5N8 only), or MF59. Healthy adult male and female (non-pregnant) participants, aged 18 years and older, will be screened for baseline health status to ensure trial eligibility. Participants meeting all the inclusion and none of the exclusion criteria will be randomized to receive vaccine doses as shown in the table below.

Two doses of adjuvanted vaccine separated by 21 days will be administered to approximately 1380 participants, including 780 participants 18 through 64 years old who will be randomized equally to 1 of 13 treatment groups (A, B, C, D, E, F, G, H, I, J, K, M, and N), and 600 participants ≥65 years old who will be randomized equally to 1 of 10 treatment groups (B, C, E, F, H, I, K, L, N, and O), as listed in the table below.

Antigen*	Adjuvant	Antigen Dose	Treatment Group	# of Participants	
				18-64 y	≥65 y
Egg-A/Astrakhan/3212/2020 (H5N8)	AS03A Full Dose	3.75 µg	A	60	0
		7.5 µg	B	60	60
		15 µg	C	60	60
Egg-A/Astrakhan/3212/2020 (H5N8)	AS03A Half Dose	3.75 µg	D	60	0
		7.5 µg	E	60	60
		15 µg	F	60	60
Egg-A/Astrakhan/3212/2020 (H5N8)	MF59	3.75 µg	G	60	0
		7.5 µg	H	60	60
		15 µg	I	60	60
Egg-A/bar-headed goose/Qinghai Lake/1A/2005 (H5N1)	AS03A Full Dose	3.75 µg	J	60	0
		7.5 µg	K	60	60
		15 µg	L	0	60
Egg-A/bar-headed goose/Qinghai Lake/1A/2005 (H5N1)	MF59	3.75 µg	M	60	0
		7.5 µg	N	60	60
		15 µg	O	0	60

*All antigens are manufactured by Sanofi.

Safety assessments will be based on solicited AEs (local and systemic reactogenicity symptoms) with onset within 8 days following each vaccination, inclusive of the vaccination day (Day 1 through Day 8 and Day 22 through Day 29); unsolicited TEAEs with onset within 22 days following each vaccination, inclusive of the vaccination day (Day 1 through Day 22 and Day 22 through Day 43); and treatment-emergent SAEs, pIMDs, and MAAEs occurring during study participation (through Day 203).

Immunogenicity assessments will include titer, seroprotection rate, and seroconversion rate based on serum HAI antibodies, and titer and seroconversion rate based on serum MN antibodies.

Study vaccines will be prepared and administered by unblinded personnel. All other trial assessments will be performed only by blinded personnel.

Number of participants (planned): Approximately 1380 healthy participants (60 or 120 participants per treatment group).

Diagnosis and main criteria for inclusion:

Participants will be randomized only if they meet all applicable inclusion criteria and none of the exclusion criteria. Deviations from inclusion and exclusion criteria are not allowed. Participants must satisfy all the Screening Criteria at study entry.

Participants, including those with exclusionary laboratory test or vital sign results, will not be rescreened.

Screening Criteria

Participant Inclusion Criteria

1. Male or non-pregnant female, 18 years of age or older at the time of screening and informed consent.
2. Willing and able to provide written informed consent prior to initiation of study procedures.
3. Agrees to have specimens collected during this trial specifically for the purpose of future research stored for future research use.
4. In relatively stable health, as determined by medical history and physical examination.
    a. Any chronic medical diagnoses or conditions should be stable and well managed, with no significant changes expected during the study period, and in the opinion of the site investigator, will not impact the ability to assess safety and/or immunogenicity per the study design.
5. If a female of childbearing potential[a] who is sexually active, agrees to use an adequate method of birth control[b] from Screening through 4 weeks following the last study vaccination and has used an adequate birth control method for at least 2 months prior to Screening.
    a. Female of childbearing potential is defined as post onset menarche and pre-menopausal person capable of becoming pregnant. This does not include females who meet any of the following conditions: a) menopausal >2 years; b) tubal ligation >1 year; c) bilateral salpingo-oophorectomy; or d) hysterectomy.
    b. Adequate contraception is defined as a contraceptive method with a failure rate of less than 1% per year when used consistently and correctly and when applicable, in accordance with the product label, for example: oral contraceptives, either combined or progestogen alone; injectable progestogen; implants of etonogestrel or levonorgestrel; estrogenic vaginal ring; percutaneous contraceptive patches; intrauterine device or intrauterine system; the female participant has exclusively female sexual partners; male partner is sterile or otherwise unable to produce sperm (information on the person's sterility can come from the site personnel's review of the participant's medical records or interview with the participant regarding her medical history); male condom combined with a vaginal spermicide (foam, gel, film, cream, or suppository); or male condom combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, film, cream, or suppository).

6. Available for all study visits, willing to participate in all study procedures, and not planning to relocate from the area for the duration of the study.

Participant Exclusion Criteria

1. Has an acute illness, as determined by the site investigator, within 72 hours prior to vaccination.
    a. An acute illness that is nearly resolved, with only minor residual symptoms remaining, is allowable if, in the opinion of the site investigator, the residual symptoms will not interfere with the ability of study staff to assess safety parameters as required by the protocol.
2. Has a history of severe reaction to any influenza vaccine.
3. Has a known allergy to squalene-based adjuvants.
4. Female of childbearing potential who has a positive urine pregnancy test or who is currently breastfeeding.
5. Has a body mass index >35 kg/m^2.
6. Has known human immunodeficiency virus, hepatitis B, or hepatitis C infection (based on medical history).
7. Has a history of any pIMDs (list provided in Protocol Appendix 3), neuralgia, paresthesia, neuritis, convulsions, or encephalomyelitis within 90 days prior to Screening, or a family history of Guillain-Barré syndrome.
8. Has narcolepsy or a first degree relative with narcolepsy.
9. Has a history of alcohol or drug abuse within 5 years prior to Screening.
10. Has any diagnosis, current or past, of schizophrenia, bipolar disease, or any other psychiatric diagnosis that may, in the opinion of the site investigator, interfere with participant compliance or safety evaluations.
11. Is immunosuppressed due to an underlying disease or medication, use of anticancer chemotherapy (cytotoxic), or radiation therapy.
12. With the exception of basal or squamous cell skin cancer, has known active neoplastic disease, including hematologic malignancy.
13. Has long-term use (≥14 consecutive days) of glucocorticoids including oral or parenteral prednisone or prednisone equivalent (>20 mg total dose per day) or high-dose inhaled steroids (>800 µg/day of beclomethasone dipropionate or equivalent) within 1 month prior to screening in this study. However, participants on low-dose inhaled steroids (≤800 µg/day of beclomethasone dipropionate or equivalent) or topical steroids are not excluded.
14. Has received immunoglobulin or other blood product (with the exception of Rho[D] immune globulin) within the 90 days prior to screening in this study.
15. Has received any (licensed or under Emergency Use Authorization [EUA]) live vaccines within 4 weeks or inactivated, messenger RNA (mRNA), or recombinant protein vaccines within 2 weeks prior to screening, or plans to receive such vaccines (including seasonal influenza and COVID-19 vaccines)

from screening through 22 days following the second dose of the study vaccine, inclusive of the vaccination day (Screening Visit through Day 43).

16. Is participating or plans to participate in another interventional clinical trial (either active or follow-up phase) during the study period.
17. Has participated in an A(H5) influenza vaccine study in the past or has a history of A(H5) influenza infection prior to vaccination in this study. This includes, but is not limited to, influenza sub-types A(H5N1), A(H5N8), and A(H5N6).
18. Has any laboratory test result or clinical findings (including vital signs) that singly or in combination are likely to unfavorably alter the risks of participant participation or to confound study safety or immunogenicity results, in the opinion of the site investigator. Additionally, the following are exclusionary:
    a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 times the upper limit of normal (ULN), or
    b. Bilirubin >1.5 times the ULN unless isolated Gilbert's syndrome.
19. Has any disease or medical condition that, in the opinion of the site investigator, might confound interpretation of safety or immunogenicity.

Vaccination Eligibility Criteria

The Vaccination Eligibility Criteria must be reviewed with each participant just prior to each vaccination; if the participant no longer meets eligibility criteria at the time of the second vaccination, the site investigator will consult with the medical monitor to determine whether the participant should receive the second vaccine dose or be terminated from further vaccination.

The most recent laboratory and vital sign results will be used when determining eligibility for the second vaccination. Any abnormal laboratory results that would be exclusionary or could be considered clinically significant should be followed up as soon as possible by resampling at an Unscheduled Visit. An acceptable result upon resampling may replace the previous abnormal laboratory result for purposes of evaluating the Vaccination Eligibility Criteria.

Participants meeting any of the rules for Early Termination of Dosing for an Individual Participant (Section 7.4.1 of the protocol) will not be eligible for the second vaccine dose.

Inclusion Criteria for Vaccination Eligibility

1. In relatively stable health, as determined by recent health history, current health, and targeted physical examination.
    a. Any chronic medical diagnoses or conditions should be stable and well managed, with no significant changes expected during the study period, and in the opinion of the site investigator, will not impact the ability to assess safety and/or immunogenicity per the study design.
2. If a female of childbearing potential who is sexually active, continued use of an adequate method of birth control (see Screening Inclusion Criteria for definitions) through 4 weeks following the last study vaccination.

Exclusion Criteria for Vaccination Eligibility

1. Has an acute illness, as determined by the site investigator, within 72 hours prior to vaccination.
    a. An acute illness that is nearly resolved, with only minor residual symptoms remaining, is allowable if, in the opinion of the site investigator, the residual symptoms will not interfere with the ability of study staff to assess safety parameters as required by the protocol.
    b. Prior to the second vaccination, if the participant's temperature is above 100.4°F, indicating illness, the participant may be re-assessed for eligibility a minimum of 24 hours later.
2. Female of childbearing potential who has a positive urine pregnancy test within the 24 hours prior to any vaccination or who is currently breastfeeding.
3. Has long-term use (≥14 consecutive days) of glucocorticoids including oral or parenteral prednisone or prednisone equivalent (>20 mg total dose per day) or high-dose inhaled steroids (>800 µg/day of beclomethasone dipropionate or equivalent) within 1 month prior to vaccination. However, participants on low-dose inhaled steroids (≤800 µg/day of beclomethasone dipropionate or equivalent) or topical steroids are not excluded.
4. Has received any (licensed or under EUA) live vaccines within 4 weeks or inactivated, mRNA, or recombinant protein vaccines within 2 weeks of the current visit.
5. Has any laboratory test result or clinical findings (including vital signs) that singly or in combination are likely to unfavorably alter the risks of participant participation or to confound study safety or immunogenicity results, in the opinion of the site investigator. Additionally, the following are exclusionary:
    a. ALT or AST >2 times the ULN, or
    b. Bilirubin >1.5 times the ULN, unless isolated Gilbert's syndrome.
6. Has any disease or medical condition that, in the opinion of the site investigator, might confound interpretation of safety or immunogenicity.

Investigational product, dosage and mode of administration:

The H5N8 vaccines will be administered at three antigen dose levels (3.75, 7.5, and 15 µg) adjuvanted with AS03A full dose, AS03A half dose, or MF59, prepared as follows:

- Mixing H5N8 influenza vaccine antigen 1:1 with AS03A adjuvant for groups receiving a full dose of AS03A; or
- Mixing H5N8 influenza vaccine antigen 1:0.5 with AS03A adjuvant for groups receiving a half dose of AS03A; or
- Mixing H5N8 influenza vaccine antigen 1:1 with MF59 adjuvant.

The H5N1 vaccines will be administered at three antigen dose levels (3.75, 7.5, and 15 µg) adjuvanted with AS03A full dose or MF59, prepared as follows:

- Mixing H5N1 influenza vaccine antigen 1:1 with AS03A adjuvant for the groups receiving a full dose of AS03A and 3.75 or 7.5 µg H5N1; or
- Mixing H5N1 influenza vaccine antigen 1:1 with MF59 adjuvant for the groups receiving 3.75 or 7.5 µg H5N1; or
- Mixing H5N1 influenza vaccine antigen 1:0.5 with AS03A adjuvant for the groups receiving a full dose of AS03A and 15 µg H5N1; or
- Mixing H5N1 influenza vaccine antigen 1:0.5 with MF59 adjuvant for the groups receiving 15 µg H5N1.

The study vaccine (0.375 mL, 0.5 mL, or 0.75 mL, depending on treatment group) will be administered by IM injection in the deltoid muscle of the arm within 30 minutes of mixing. The 2 vaccine doses for an individual participant should be given in alternate arms. Vaccine doses can be administered in the same arm if a skin condition prevents administration in one of the arms (e.g., scar tissue, skin rash, etc.).

Duration of treatment:

Participants will receive vaccine doses based on their assigned treatment group at approximately Day 1 and Day 22 and will be followed to approximately Day 203. The expected study duration is approximately 7 months per participant.

Reference therapy, dosage and mode of administration: Not applicable

Criteria for evaluation:

Immunogenicity

- Serum HAI antibody titers
- Seroprotection based on serum HAI antibody titers, defined as an HAI antibody titer ≥1:40
- Seroconversion based on serum HAI antibody titers, defined as either a pre-vaccination HAI titer <1:10 and a post-vaccination HAI titer ≥1:40, or a pre-vaccination HAI titer ≥1:10 and a minimum 4-fold rise in post-vaccination HAI titer
- Serum MN antibody titers
- Seroconversion based on serum MN antibody titers, defined as either a pre-vaccination MN titer <1:10 and a post-vaccination MN titer ≥1:40, or a pre-vaccination MN titer ≥1:10 and a minimum 4-fold rise in post-vaccination MN titer

Immune responses for each vaccine regimen in terms of HAI and MN antibody responses will be evaluated against H5N8 and H5N1

Safety

Safety will be evaluated by assessing frequency and severity of solicited local and systemic reactogenicity symptoms occurring within 8 days following each vaccination, inclusive of the vaccination day (Day 1 through Day 8 and Day 22 through Day 29),

unsolicited TEAEs occurring within 22 days following each vaccination, inclusive of the vaccination day (Day 1 through Day 22 and Day 22 through Day 43), and treatment-emergent SAEs, MAAEs, and pIMDs occurring during study participation (through Day 203). Safety assessments will also include physical examination, vital signs, and clinical laboratory tests (hematology and chemistry).

Study Endpoints:

Primary Endpoints

Primary Safety Endpoints:

- The percentage of participants who experience any solicited local reactogenicity symptom occurring within 8 days of each vaccination, inclusive of the vaccination day (Day 1 through Day 8 and Day 22 through Day 29).
- The percentage of participants who experience any solicited systemic reactogenicity symptom occurring within 8 days of each vaccination, inclusive of the vaccination day (Day 1 through Day 8 and Day 22 through Day 29).

Primary Immunogenicity Endpoint

- The percentage of participants achieving seroprotection at Day 43 based on serum HAI antibody titers (≥1:40) to A/Astrakhan (H5N8).

Secondary Endpoints

Secondary Safety Endpoints

- The percentage of participants who experience any unsolicited TEAE within 22 days of each vaccination, inclusive of the vaccination day (Day 1 through Day 22 and Day 22 through Day 43).
- The percentage of participants who experience any treatment-emergent SAE through Day 203.
- The percentage of participants who experience any treatment-emergent MAAE through Day 203.
- The percentage of participants who experience any treatment-emergent pIMD through Day 203.

Secondary Immunogenicity Endpoints

- The percentage of participants achieving seroprotection at Day 43 based on serum HAI antibody titers (≥1:40) to A/bar-headed goose (H5N1).

Immune responses for each vaccine regimen in terms of HAI and MN antibody responses against the H5N8 and H5N1 strains by:

- Serum HAI antibody titers at Screening and Days 22, 43, and 203.

- The percentage of participants achieving seroprotection at Days 22 and 203 based on serum HAI antibody titers (≥ 1:40).
- The percentage of participants achieving seroconversion at Days 22, 43, and 203 based on serum HAI antibody titers.
- Serum MN antibody titers at Screening and Days 22, 43, and 203.
- The percentage of participants achieving seroconversion at Days 22, 43, and 203 based on serum MN antibody titers.

Statistical methods:

Analysis Plan

Due to the exploratory nature of this study, no formal power analysis was conducted, and no formal hypothesis testing is planned. Descriptive statistics (such as means, standard deviations, geometric means [for immunogenicity data only], medians, quartiles, and ranges for continuous data, and percentages for categorical data) will be used to summarize participant characteristics, safety, and immunogenicity parameters. These summaries will be presented overall (as applicable) and separately for the participants in the different treatment groups, as well as pooled groups by antigen, antigen dose level, and by adjuvant, as appropriate. Details of the statistical analyses, methods, and data conventions will be described in the Statistical Analysis Plan (SAP).

Interim Analysis

An interim analysis will be performed based on available cumulative immunogenicity and safety data through Day 43 for all participants. At the time of the interim analysis, the study database (all data through Day 43) will be monitored and cleaned per the associated study plans. The unblinded Day 43 analysis will be compiled by an unblinded statistical team to ensure the blind will be maintained until the study unblinding of all data at the end of study. Further details will be specified in the SAP.

Ad Hoc Safety Monitoring Committee (SMC) Meeting

There are no formal or planned SMC meetings. An SMC review will only occur when 1 or more of the findings leading to study suspension are met or for any immediate safety concerns observed. Data displays for any SMC review will be generated by the appropriate blinded or unblinded statistical team. The operations of the SMC will be specified in the SMC charter.

Final Analyses

The final analyses will include all safety and immunogenicity data through the end of study. The study database will be monitored and cleaned per the associated study plans. Study data will be unblinded to prepare the final analyses. Cumulative summaries of all SAEs, MAAEs, and pIMDs occurring from Day 1 through the end of study will be included. Further details will be specified in the SAP.

Analysis Populations

Safety Population

The safety population will include all participants who are randomized and receive at least one vaccination. For individual safety summaries of each vaccine dose, each participant will be analyzed as part of the treatment group corresponding to the actual treatment received for the applicable vaccine dose. For all other safety analyses by group, each participant will be analyzed corresponding to the actual treatment received for their first vaccine dose. The safety population will be used for all safety analyses.

Immunogenicity Full Analysis Population

The immunogenicity full analysis population (IFAP) will include all participants who are randomized, receive at least one vaccination, and have determinate assay results at any post-vaccination visit. Each participant will be analyzed as part of the treatment group assigned by randomization, regardless of the treatment actually received. All immunogenicity analyses will be performed on the IFAP.

Immunogenicity Per Protocol Population

The immunogenicity per protocol population (IPPP) will include all participants who meet the following criteria:

- Are in the IFAP.
- Received a full dose of vaccine at Day 1 and a full dose of vaccine at Day 22.
- Received the correct treatment as assigned by randomization.
- Have no other major protocol deviations that may have an impact on immunogenicity assessments.
- Have determinate assay results at the Day 43 visit.

All immunogenicity analyses will also be performed on the IPPP.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse event
ALT	Alanine aminotransferase
APHIS	Animal and Plant Health Inspection Service
ASPR	Administration for Strategic Preparedness and Response
AST	Aspartate aminotransferase
BARDA	Biomedical Advanced Research and Development Authority
BMI	Body mass index
CBC	Complete blood count
CFR	Code of Federal Regulations
CI	Confidence interval
CICP	Countermeasures Injury Compensation Program
eCRF	Electronic Case Report Form
EoS	End of Study
ET	Early Termination
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
GCLP	Good Clinical Laboratory Practice
GCP	Good Clinical Practice
GMT	Geometric mean titer
HA	Hemagglutinin
HAI	Hemagglutination-inhibition
HHS	Health and Human Services
HPAI	Highly pathogenic avian influenza
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICON	ICON plc
IEC	Independent Ethics Committee
IFAP	Immunogenicity full analysis population
IM	Intramuscular(ly)

Abbreviation or Specialist Term	Explanation
IPPP	Immunogenicity per protocol population
IRB	Institutional Review Board
MAAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger RNA
MN	Microneutralization
MOP	Manual of Procedures
NPIVS	National Pre-Pandemic Influenza Vaccine Stockpile
OTC	Over the counter
pIMD	Potentially immune-mediated disease
PREP	Public Readiness and Emergency Preparedness
QA	Quality assurance
QC	Quality control
RT-PCR	Reverse transcription-polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAR	Suspected Adverse Reaction
SE	Stable oil-in-water emulsion
SMC	Safety Monitoring Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States
USDA	United States Department of Agriculture

5. INTRODUCTION

5.1. Rationale

Highly pathogenic avian influenza A(H5) viruses, predominantly HPAI A(H5N1) clade 2.3.4.4b viruses, have been circulating globally in wild birds in the U.S. since late 2021. These viruses have caused outbreaks in commercial and backyard poultry, with spillover resulting in sporadic infections in mammals. As of March 29, 2024, USDA's Animal and Plant Health Inspection Service (APHIS) confirmed the detection of highly pathogenic avian influenza (HPAI) in dairy herds, with wild migratory birds believed to be the source of infection. With the first reported human case of Influenza A(H5N1) clade 2.3.4.4b virus in the U.S. in late April 2022 and a more recent human case in Texas in April 2024, it is crucial that preparation be maintained to enable rapid response and successful commercial scale production of vaccine if needed for a pandemic event.

The overall goal of this randomized, double-blind, phase 2 trial is to identify one or more combinations of vaccine and adjuvant that exhibit safety and immunological characteristics likely to predict benefit in the event of an emerging H5 pandemic. The trial is designed to further inform options for strategic deployment of pre-pandemic influenza vaccines in the National Pre-Pandemic Influenza Vaccine Stockpile (NPIVS). This trial will obtain safety and immunogenicity data following administration of egg-based Influenza A(H5N1) clade 2.2 and egg-based Influenza A(H5N8) clade 2.3.4.4b antigens adjuvanted with full-dose AS03A, half-dose AS03A (H5N8 only), or MF59. In an earlier study (BP-I-16-005)[1], boosting subjects who previously received two doses of A/Gyrfalcon (H5N8) clade 2.3.4.4 vaccine with a third dose of A/bar-headed goose (H5N1) generated seroprotection rates of 82% (71, 93) with a GMT of 111 (75, 162) against A/Gyrfalcon (H5N8), suggesting that A/bar-headed goose (H5N1) might be able to generate protective antibody responses against the current circulating threat clade. A/Astrakhan (H5N8) clade 2.3.4.4.b matches the current threat clade and will be tested in antigen and adjuvant-sparing vaccine regimens for pandemic preparedness, whereas A/bar-headed goose (H5N1) clade 2.2 will be tested in antigen-sparing vaccine regimens. Given the current HPAI A/H5 context in the United States, response to A/Astrakhan (H5N8) is the primary endpoint. Antigenic analysis indicates clade 2.3.4.4b A/Astrakhan/3212/2020 (H5N8) cross-reacts with H5N1 viruses circulating in the US, making it an excellent candidate for development of vaccines to increase H5 pandemic preparedness.

In the event of a public health emergency, data from this trial will be utilized to determine potential vaccination strategies, including antigen-sparing strategies to extend the antigen supply and support a potential Emergency Use Authorization (EUA) or a license application.

5.2. Investigational Products

5.2.1. Egg-A/Astrakhan/3212/2020 (H5N8)

Egg-A/Astrakhan/3212/2020 (H5N8) is prepared from A/Astrakhan/3212/2020 (H5N8) candidate vaccine virus propagated in embryonated chicken eggs, employing the same technology used to make Sanofi seasonal influenza vaccines such as Fluzone® Quadrivalent.[2]

No clinical data are available for Egg-A/Astrakhan/3212/2020 (H5N8). However, clinical information is provided through four phase 2 clinical studies performed by the National Institutes

of Health to evaluate egg-based monovalent H7N9 influenza vaccine manufactured according to the process described above, derived from A/Shanghai/2/2013 (H7N9), mixed on site with 2 different adjuvants known to improve the immunogenicity of other inactivated influenza vaccines.[3]

The first study (DMID 13-0032) was conducted in adults aged 19 through 64 years, with adjuvanted H7N9 antigen through HHS BARDA.[4,5] The study showed that following administration of 2 doses of MF59-adjuvanted vaccine, seroconversion was achieved in 59% of participants. The second study (DMID 13-0033) conducted in adults aged 19 through 64 years showed that following 2 doses of AS03-adjuvanted vaccine, hemagglutination-inhibition (HAI) antibody titers of ≥1:40 were induced in at least 81% of participants.[3,6] The third study (DMID 13-0034) showed that in elderly participants (65 years and older), very modest serum antibody responses were generated following administration of 2 doses of MF59-adjuvanted vaccine.[7] The addition of a third dose of MF59-adjuvanted vaccine had modest impact with seroconversion rates still being quite low, ranging from 32% to 46%. The fourth study (DMID 13-0044) was conducted in 27 adults aged 19 through 50 years and showed that participants who received unadjuvanted A/H7N9 monovalent egg-based split-virion inactivated influenza vaccine in a previous trial in 2008 were primed to improved immune response to 1 dose of unadjuvanted A/H7N9 monovalent egg-based split-virion inactivated influenza vaccine at the 45 µg hemagglutinin dosage, compared to influenza A/H7-naïve persons.[8-10]

In all four studies, the administered H7N9 vaccines were well tolerated and provided important immunogenicity information for the continued development of influenza pandemic preparedness programs.

5.2.2. Egg-A/bar-headed goose/Qinghai Lake/1A/2005 (H5N1)

Egg-A/bar-headed goose/Qinghai Lake/1A/2005 (H5N1) is prepared from A/bar-headed goose/Qinghai Lake/1A/2005 (H5N1) propagated in embryonated chicken eggs, employing the same technology used to make Sanofi seasonal influenza vaccines such as Fluzone® Quadrivalent.[2]

In addition to the various data cited above for egg-based monovalent H7N9 influenza vaccine manufactured according to the technology described, Egg-A/bar-headed goose/Qinghai Lake/1A/2005 (H5N1) was previously included as a booster dose following heterologous priming doses with other H5 vaccines in a BARDA-sponsored study (BP-I-16-005) to assess the safety and immunogenicity of various homologous or heterologous prime-boost or prime-prime-boost series with inactivated monovalent influenza H5 vaccines.[1] A total of 242 participants were randomized to receive Egg-A/bar-headed goose/Qinghai Lake/1A/2005 (H5N1) as the booster dose (Dose #3). The booster dose elicited a robust immune response as demonstrated via a high serum HAI antibody seroprotection rate, with increased breadth of cross-reactive immunogenicity at Day 163, 21 days after the booster dose. The Egg-A/bar-headed goose/Qinghai Lake/1A/2005 (H5N1) antigen was considered to be well tolerated. No deaths or serious adverse events (SAEs) related to vaccination were observed, and there were no notable trends in clinical laboratory results or vital signs. This study will evaluate Egg-A/bar-headed goose/Qinghai Lake/1A/2005 (H5N1) as a priming H5N1 vaccine to further inform vaccination strategies for responding to a pandemic influenza public health emergency.

5.2.3. Adjuvants: AS03A and MF59

The MF59 (CSL Seqirus) adjuvant is an oil-in-water emulsion composed of squalene, stabilized by the addition of two emulsifiers, polysorbate 80 and sorbitan trioleate (Span 51), and a low ionic strength buffer. MF59-adjuvanted influenza vaccines have been licensed in the US (FLUAD™ and AUDENZ™ vaccine).[11,12]

The AS03A (GSK) adjuvant is an oil-in-water emulsion containing DL-α-tocopherol, squalene, polysorbate 80, and a buffer. AS03A is the adjuvant AS03®. AS03-adjuvanted vaccines have been licensed in the US and have a large safety dataset.[13,14]

5.3. Risks

5.3.1. Antigens: Egg-A/Astrakhan/3212/2020 (H5N8) and Egg-A/bar-headed goose/Qinghai Lake/1A/2005 (H5N1)

Possible reactions to any parenteral immunization include local reactions such as swelling, warmth, induration, soreness and erythema at the site of injection, as well as systemic reactions such as fever, malaise, fatigue, headache, nausea, myalgia, and arthralgia. Guillain-Barré syndrome has been associated with some influenza vaccines, although the mechanism of this adverse event is unclear. Although the likelihood is minimal, allergy to any component of the influenza vaccine, such as residual egg protein, may trigger an anaphylactic reaction that can result in death if not promptly treated.

5.3.2. Adjuvants: AS03A and MF59

There are no major safety concerns associated with the use of adjuvants AS03A and MF59; however, there is epidemiological evidence of an association between influenza vaccine adjuvanted with AS03 and narcolepsy. In studies of influenza A(H1N1) vaccine adjuvanted with AS03, there was a small increased risk of narcolepsy in participants who received adjuvanted vaccine; however, narcolepsy developed almost exclusively in the pediatric population vaccinated with influenza A(H1N1) adjuvanted with AS03 (Pandemrix, GSK, Wavre, Belgium, produced in Dresden, Germany) and primarily in Scandinavian countries.[15,16] A small study to assess the risk of narcolepsy following administration of a similar vaccine adjuvanted with AS03 (Arepanrix, GSK, Wavre, Belgium, produced in Quebec City, Canada) was performed in Quebec, Canada.[17] The Canadian study showed a small risk of developing narcolepsy after receiving the AS03 adjuvanted A(H1N1) pandemic vaccine manufactured in Quebec. This risk occurred primarily in people less than 20 years of age and was much less than that seen in some European countries. There was also a study conducted by the Centers for Disease Control "SOMNIA study" that assessed the risk of narcolepsy following administration of adjuvanted 2009 H1N1 pandemic vaccines. Comparison of incidence rates of narcolepsy before, during, and after the use of adjuvanted 2009 pandemic influenza vaccines provided no evidence outside of the signaling country Sweden.[18]

Adjuvants, including AS03A and MF59, are used in vaccine formulations as potent inducers of the immune system. There exists a theoretical potential for induction of autoimmune or autoinflammatory diseases. Appropriate safety monitoring for such events is included in this trial and detailed in Section 12.2.1.4 and Section 12.2.1.5.

5.4. Benefits

There are no anticipated benefits to the individual participants of this trial.

The safety and immunogenicity of egg-based vaccines administered with AS03A and MF59 adjuvants are well supported by previous clinical trials. The safety and immunogenicity data acquired through this trial will be used to determine potential vaccination strategies in the event of a public health emergency.

6. STUDY OBJECTIVES

Table 2: Study Objectives and Endpoints

Objectives	Endpoints
Primary Safety	
• To assess the safety and reactogenicity for 8 days following each vaccination, inclusive of the vaccination day (Day 1 through Day 8 and Day 22 through Day 29) of different antigens and antigen doses of vaccine given with AS03A full dose, AS03A half dose, or MF59 adjuvant administered intramuscularly (IM) on Days 1 and 22, as determined by solicited local and systemic reactogenicity symptoms.	• The percentage of participants who experience any solicited local reactogenicity symptom occurring within 8 days of each vaccination, inclusive of the vaccination day (Day 1 through Day 8 and Day 22 through Day 29). • The percentage of participants who experience any solicited systemic reactogenicity symptom occurring within 8 days of each vaccination, inclusive of the vaccination day (Day 1 through Day 8 and Day 22 through Day 29).
Primary Immunogenicity	
• To assess the serum hemagglutination-inhibition (HAI) antibody seroprotection rate on Day 43, following IM administration of the study vaccines on Days 1 and 22.	• The percentage of participants achieving seroprotection at Day 43 based on serum HAI antibody titers (≥1:40) to A/Astrakhan (H5N8).
Secondary Safety	
• To assess the occurrence of any unsolicited treatment-emergent adverse events (TEAEs) within 22 days following each vaccination, inclusive of the vaccination day (Day 1 through Day 22 and Day 22 through Day 43) for the study vaccines. • To assess the occurrence of treatment-emergent SAEs and medically attended adverse events (MAAEs), including a subset of specific potentially immune-mediated diseases (pIMDs), for the study vaccines through Day 203.	• The percentage of participants who experience any unsolicited TEAE within 22 days of each vaccination, inclusive of the vaccination day (Day 1 through Day 22 and Day 22 through Day 43). • The percentage of participants who experience any treatment-emergent SAE through Day 203. • The percentage of participants who experience any treatment-emergent MAAE through Day 203. • The percentage of participants who experience any treatment-emergent pIMD through Day 203.
Secondary Immunogenicity	
• To assess the serum HAI antibody titers, seroprotection rates, and seroconversion rates elicited by the study vaccines through Day 203.	The percentage of participants achieving seroprotection at Day 43 based on serum HAI antibody titers (≥1:40) to A/bar-headed goose (H5N1). Immune responses for each vaccine

Objectives	Endpoints
• To assess the serum microneutralization (MN) antibody titers and seroconversion rates elicited by the study vaccines through Day 203.	regimen in terms of HAI and MN antibody responses against the H5N8 and H5N1 strains by: • Serum HAI antibody titers at Screening and Days 22, 43, and 203. • The percentage of participants achieving seroprotection at Days 22 and 203 based on serum HAI antibody titers (≥ 1:40). • The percentage of participants achieving seroconversion at Days 22, 43, and 203 based on serum HAI antibody titers. • Serum MN antibody titers at Screening and Days 22, 43, and 203. • The percentage of participants achieving seroconversion at Days 22, 43, and 203 based on serum MN antibody titers.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a randomized, double-blind, phase 2 study to assess safety and immunogenicity of egg-based H5N8 and H5N1 influenza vaccines at different antigen dose levels (3.75, 7.5, and 15 µg) adjuvanted with AS03A full dose, AS03A half dose (H5N8 only), or MF59. Approximately 1380 male and nonpregnant female adults, including approximately 780 participants ages 18 through 64 years old and approximately 600 participants ≥65 years old, will be enrolled in the study (Section 7.2).

Figure 1 presents a diagram of the overall study design. After screening, participants meeting all of the inclusion and none of the exclusion criteria will receive 2 intramuscular (IM) vaccinations in total. Vaccinations will be administered on Days 1 and 22. Participants will receive either egg-based H5N8 or H5N1 influenza vaccines at different antigen dose levels (3.75, 7.5, or 15 µg) adjuvanted with AS03A full dose, AS03A half dose (H5N8 only), or MF59, based on their assigned treatment group. Participants 18 through 64 years old will be randomized equally to 1 of 13 treatment groups, and participants ≥65 years old will be randomized equally to 1 of 10 treatment groups. Treatment group assignments are shown in Table 3.

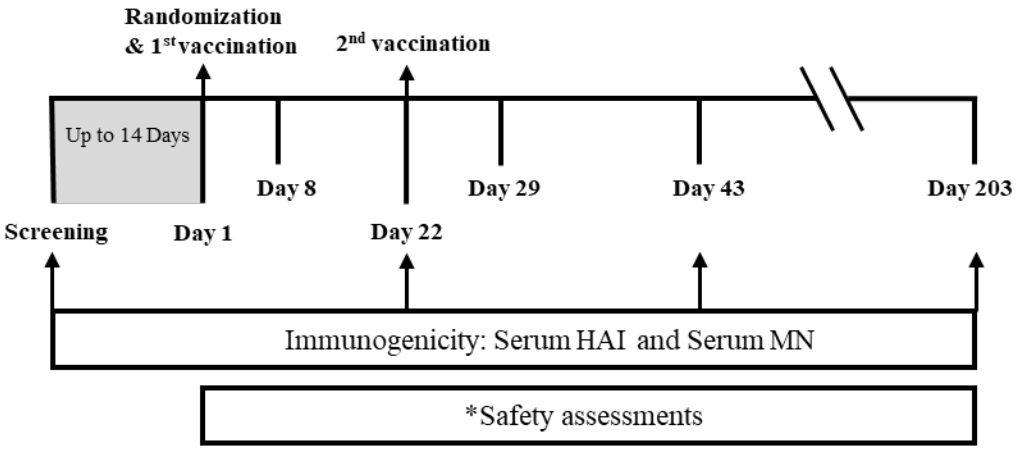
Safety assessments will be based on solicited AEs (local and systemic reactogenicity symptoms) with onset within 8 days following each vaccination, inclusive of the vaccination day (Day 1 through Day 8 and Day 22 through Day 29); unsolicited treatment-emergent adverse events (TEAEs) with onset within 22 days following each vaccination, inclusive of the vaccination day (Day 1 through Day 22 and Day 22 through Day 43); and treatment-emergent SAEs, potentially immune-mediated diseases (pIMDs), and medically attended adverse event (MAAEs) occurring during study participation. For this study, a pIMD is considered to be unexpected and will be treated as a suspected unexpected serious adverse reaction (SUSAR) per 21 CFR 312.32. Section 12 provides a detailed description of the safety parameters to be assessed during the study.

Sera from all groups will be tested against A/Astrakhan (H5N8) and A/bar-headed goose (H5N1). Immunogenicity assessments will include serum HAI titers, serum microneutralization (MN) titers, seroprotection rate, and seroconversion rate based on serum HAI titers, and seroconversion rate based on serum MN titers. Additional details regarding the immunogenicity assessments are presented in Section 11.

The expected study duration is approximately 203 days per participant.

The Schedule of Assessments can be found in Appendix 1.

Figure 1: Overall Study Design



AE=adverse event; HAI=hemagglutination inhibition; MN=microneutralization
*AEs will be assessed from the time the participant receives the first study vaccine dose as summarized in Figure 2.

7.2. Number of Participants

The proposed enrollment for this study is approximately 1380 participants, including approximately 780 participants 18 through 64 years old and approximately 600 participants ≥65 years old.

7.3. Treatment Assignment

Participants will receive 2 IM injections of adjuvanted vaccine separated by 21 days. Participants will receive either egg-based H5N8 or H5N1 influenza vaccines at different antigen dose levels (3.75, 7.5, or 15 µg) adjuvanted with AS03A full dose, AS03A half dose (H5N8 only), or MF59. Participants 18 through 64 years old will be randomized equally to 1of 13 treatment groups (A, B, C, D, E, F, G, H, I, J, K, M, and N), and participants ≥65 years old will be randomized equally to 1 of 10 treatment groups (B, C, E, F, H, I, K, L, N, and O), as listed in Table 3.

Table 3: Treatment Groups

Antigen*	Adjuvant	Antigen Dose	Treatment Group	# of Participants	
				18-64 y	≥65 y
Egg-A/Astrakhan/3212/2020 (H5N8)	AS03A Full Dose	3.75 µg	A	60	0
		7.5 µg	B	60	60
		15 µg	C	60	60
Egg-A/Astrakhan/3212/2020 (H5N8)	AS03A Half Dose	3.75 µg	D	60	0
		7.5 µg	E	60	60
		15 µg	F	60	60
Egg-A/Astrakhan/3212/2020 (H5N8)	MF59	3.75 µg	G	60	0
		7.5 µg	H	60	60
		15 µg	I	60	60
Egg-A/bar-headed goose/Qinghai Lake/1A/2005 (H5N1)	AS03A Full Dose	3.75 µg	J	60	0
		7.5 µg	K	60	60
		15 µg	L	0	60
Egg-A/bar-headed goose/Qinghai Lake/1A/2005 (H5N1)	MF59	3.75 µg	M	60	0
		7.5 µg	N	60	60
		15 µg	O	0	60

*All antigens are manufactured by Sanofi.

7.4. Individual Participant Dosing and Study Stopping Rules

7.4.1. Early Termination of Dosing for an Individual Participant

Vaccinations in a participant are to be stopped if the participant experiences any of the following and will preclude further administration of study vaccine until the specific AE can be evaluated and is shown to resolve completely. In situations of ambiguity or uncertainty, the site investigator is encouraged to discuss the situation and any questions with the medical monitor before making a decision on participant disposition.

1. Three or more occurrences of Grade 3 or higher AEs of different preferred terms (as categorized by the Medical Dictionary for Regulatory Activities [MedDRA]) assessed as at least possibly related (i.e., possibly related, probably related, or related) to study

vaccine without a plausible alternative explanation (Section 12.3.3, Section 12.4, and Appendix 2).

2. Any Grade 3 or higher MAAE assessed as at least possibly related to study vaccine without a plausible alternative explanation (Section 12.3.3, Section 12.4, and Appendix 2).
3. Any SAE or pIMD assessed as at least possibly related to study vaccine without a plausible alternative explanation (Section 12.4 and Appendix 3).
4. Any Grade 3 or higher abnormal laboratory test result that, in the opinion of the site investigator or medical monitor, is clinically significant, and that is assessed as at least possibly related to study vaccine without a plausible alternative explanation (Section 12.2.1, Section 12.3.3, Section 12.4, and Appendix 2). Note: All Grade 3 or higher abnormal laboratory test results, whether considered related or unrelated to study vaccine, must be discussed with the medical monitor.
5. Anaphylaxis.
6. Grade 3 or higher allergic reaction, as judged by the site investigator (such as, but not limited to, difficulty breathing, rapid increase in heart rate, dizziness, nausea, evidence of urticaria, or periorbital swelling) assessed as at least possibly related to study vaccine without a plausible alternative explanation.
7. Intolerable AE that is assessed as at least possibly related to study vaccine without a plausible alternative explanation.
8. Participant no longer meets eligibility criteria, such that safety of the participant may be compromised by continued participation or interpretation of the participant's subsequent study data is likely to be significantly compromised.
9. Any other condition that, in the judgment of the site investigator, would make further vaccination unsafe or render the participant unable to comply with protocol-mandated safety follow-up.

A participant who does not receive the second vaccination will continue to be followed for safety and immunogenicity through the End of Study (EoS) Visit (Visit 6) on approximately Day 203 (Appendix 1). A participant who becomes pregnant during the study will be followed for safety only and will not provide blood for the immunogenicity assays. Additional clinical laboratory assessments will be completed during the safety follow-up only when determined to be clinically necessary by the site investigator in consultation with the medical monitor.

7.4.2. Study Suspension and Safety Monitoring Committee Responsibility

The blinded medical monitor will assess cumulative safety information for this study per the Medical Monitoring Plan and advise BARDA should he/she become aware that any of the safety findings listed below have occurred. The occurrence and confirmation of 1 or more of the findings in Table 4 will result in suspension of further enrollment and study vaccine administration pending urgent review (within 7 days) of the safety data by the Safety Monitoring Committee (SMC).

Table 4: Findings Leading to Study Suspension

No.	**Safety Parameter**	**No. of** Participants
1	Any AE of broncho/laryngospasm or anaphylaxis occurring after each study vaccine administration that is considered at least possibly related[a] to the study vaccine.	≥2 participants
2	Any SAE, including death, occurring after each study vaccine administration that is considered at least possibly related[a] to the study vaccine.	≥1 participant
3	Any Grade 3 (severe) or higher unsolicited adverse event of a similar type occurring post-vaccination that is considered at least probably related[b] to the study vaccine.	≥10% of enrolled participants (minimum n=5)

[a] possibly related, probably related, or related to study vaccine
[b] probably related or related to study vaccine

Following their unblinded review of available safety data, the SMC will make 1 or more of the following recommendations:

- All vaccinations should resume.
- Specific treatment groups should be discontinued while other treatment groups should resume vaccinations.
- No vaccinations should resume.
- Modifications to study conduct (e.g., additional safety laboratory assessments).

As the trial sponsor, BARDA retains the right to suspend or end the study or to discontinue specific treatment groups at any time. In case of premature termination or suspension and safety review of the study, BARDA will promptly inform the site investigators and regulatory authorities as appropriate of the termination or suspension and reason for termination/suspension.

7.5. Criteria for Termination of Study Vaccinations

The study vaccinations may be prematurely terminated if there is sufficient reasonable cause, including but not limited to:

1. Determination of unexpected, significant, or unacceptable risk to participants
2. If required by Regulatory authority(ies)

If study vaccinations are prematurely terminated, the site investigator will promptly inform study participants and the Institutional Review Board (IRB) and local regulatory authorities as applicable. Study participants will be contacted, as applicable, and be informed of changes to their study visit schedule. The site investigator will ensure appropriate follow-up for the participants, as necessary.

The sponsor, BARDA, will notify regulatory authorities as applicable.

8. SELECTION AND WITHDRAWAL OF PARTICIPANTS

8.1. Selection of Study Population

This study will recruit healthy adult male and non-pregnant female participants, aged 18 years and older. It is not known whether the study vaccines used in this study may cause fetal harm, so pregnant women will not be included.

Participants will be randomized only if they meet all applicable inclusion criteria and none of the exclusion criteria. Deviations from inclusion and exclusion criteria are not allowed. Participants must satisfy all the Screening Criteria at study entry.

Participants, including those with exclusionary laboratory test or vital sign results, will not be rescreened.

8.1.1. Screening Criteria

These criteria will be assessed at the time of Screening.

8.1.1.1. Participant Inclusion Criteria (Screening)

1. Male or non-pregnant female, 18 years of age or older at the time of screening and informed consent.
2. Willing and able to provide written informed consent prior to initiation of study procedures.
3. Agrees to have specimens collected during this trial specifically for the purpose of future research stored for future research use.
4. In relatively stable health, as determined by medical history and physical examination.
    a. Any chronic medical diagnoses or conditions should be stable and well managed, with no significant changes expected during the study period, and in the opinion of the site investigator, will not impact the ability to assess safety and/or immunogenicity per the study design.
5. If a female of childbearing potential[a] who is sexually active, agrees to use an adequate method of birth control[b] from Screening through 4 weeks following the last study vaccination and has used an acceptable birth control method for at least 2 months prior to Screening.
    a. Female of childbearing potential is defined as post onset menarche and pre-menopausal person capable of becoming pregnant. This does not include females who meet any of the following conditions: a) menopausal >2 years; b) tubal ligation >1 year; c) bilateral salpingo-oophorectomy; or d) hysterectomy.
    b. Adequate contraception is defined as a contraceptive method with a failure rate of less than 1% per year when used consistently and correctly and when applicable, in accordance with the product label, for example: oral contraceptives, either combined or progestogen alone; injectable progestogen; implants of etonogestrel or levonorgestrel; estrogenic vaginal ring; percutaneous contraceptive patches; intrauterine device or intrauterine system; the female participant has exclusively

female sexual partners; male partner is sterile or otherwise unable to produce sperm (information on the person's sterility can come from the site personnel's review of the participant's medical records or interview with the participant regarding her medical history); male condom combined with a vaginal spermicide (foam, gel, film, cream, or suppository); or male condom combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, film, cream, or suppository).

6. Available for all study visits, willing to participate in all study procedures, and not planning to relocate from the area for the duration of the study.

8.1.1.2. Participant Exclusion Criteria (Screening)

1. Has an acute illness, as determined by the site investigator, within 72 hours prior to vaccination.
    a. An acute illness that is nearly resolved, with only minor residual symptoms remaining, is allowable if, in the opinion of the site investigator, the residual symptoms will not interfere with the ability of study staff to assess safety parameters as required by the protocol.
2. Has a history of severe reaction to any influenza vaccine.
3. Has a known allergy to squalene-based adjuvants.
4. Female of childbearing potential who has a positive urine pregnancy test or who is currently breastfeeding.
5. Has a body mass index >35 kg/m^2.
6. Has known human immunodeficiency virus, hepatitis B, or hepatitis C infection (based on medical history).
7. Has a history of any pIMDs (list provided in Appendix 3), neuralgia, paresthesia, neuritis, convulsions, or encephalomyelitis within 90 days prior to Screening, or a family history of Guillain-Barré syndrome.
8. Has narcolepsy or a first degree relative with narcolepsy.
9. Has a history of alcohol or drug abuse within 5 years prior to Screening.
10. Has any diagnosis, current or past, of schizophrenia, bipolar disease, or any other psychiatric diagnosis that may, in the opinion of the site investigator, interfere with participant compliance or safety evaluations.
11. Is immunosuppressed due to an underlying disease or medication, use of anticancer chemotherapy (cytotoxic), or radiation therapy.
12. With the exception of basal or squamous cell skin cancer, has known active neoplastic disease, including hematologic malignancy.
13. Has long-term use (≥14 consecutive days) of glucocorticoids including oral or parenteral prednisone or prednisone equivalent (>20 mg total dose per day) or high-dose inhaled steroids (>800 µg/day of beclomethasone dipropionate or equivalent) within 1 month prior to screening in this study. However, participants on low-dose inhaled steroids

(≤800 µg/day of beclomethasone dipropionate or equivalent) or topical steroids are not excluded.

14. Has received immunoglobulin or other blood product (with the exception of Rho[D] immune globulin) within the 90 days prior to screening in this study.
15. Has received any (licensed or under Emergency Use Authorization [EUA]) live vaccines within 4 weeks or inactivated, messenger RNA (mRNA), or recombinant protein vaccines within 2 weeks prior to screening, or plans to receive such vaccines (including seasonal influenza and COVID-19 vaccines) from screening through 22 days following the second dose of the study vaccine, inclusive of the vaccination day (Screening Visit through Day 43).
16. Is participating or plans to participate in another interventional clinical trial (either active or follow-up phase) during the study period.
17. Has participated in an A(H5) influenza vaccine study in the past or has a history of A(H5) influenza infection prior to vaccination in this study. This includes, but is not limited to, influenza sub-types A(H5N1), A(H5N8), and A(H5N6).
18. Has any laboratory test result or clinical findings (including vital signs) that singly or in combination are likely to unfavorably alter the risks of participant participation or to confound study safety or immunogenicity results, in the opinion of the site investigator. Additionally, the following are exclusionary:
    a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 times the upper limit of normal (ULN), or
    b. Bilirubin >1.5 times the upper limit of normal (ULN) unless isolated Gilbert's syndrome.
19. Has any disease or medical condition that, in the opinion of the site investigator, might confound interpretation of safety or immunogenicity.

8.1.2. Vaccination Eligibility Criteria

The Vaccination Eligibility Criteria must be reviewed with each participant just prior to each vaccination; if the participant no longer meets eligibility criteria at the time of the second vaccination, the site investigator will consult with the medical monitor to determine whether the participant should receive the second vaccine dose or be terminated from further vaccination.

The most recent laboratory and vital sign results will be used when determining eligibility for the second vaccination. Any abnormal laboratory results that would be exclusionary or could be considered clinically significant should be followed up as soon as possible by resampling at an Unscheduled Visit. An acceptable result upon resampling may replace the previous abnormal laboratory result for purposes of evaluating the Vaccination Eligibility Criteria.

Participants meeting any of the rules for Early Termination of Dosing for an Individual Participant (Section 7.4.1) will not be eligible for the second vaccine dose.

8.1.2.1. Participant Inclusion Criteria (Prior to Vaccination)

1. In relatively stable health, as determined by recent health history, current health, and targeted physical examination.
    a. Any chronic medical diagnoses or conditions should be stable and well managed, with no significant changes expected during the study period, and in the opinion of the site investigator, will not impact the ability to assess safety and/or immunogenicity per the study design.
2. If a female of childbearing potential who is sexually active, continued use of an adequate method of birth control (see Screening Inclusion Criteria for definitions) through 4 weeks following the last study vaccination.

8.1.2.2. Participant Exclusion Criteria (Prior to Vaccination)

1. Has an acute illness, as determined by the site investigator, within 72 hours prior to vaccination.
    a. An acute illness that is nearly resolved, with only minor residual symptoms remaining, is allowable if, in the opinion of the site investigator, the residual symptoms will not interfere with the ability of study staff to assess safety parameters as required by the protocol.
    b. Prior to the second vaccination, if the participant's temperature is above 100.4°F, indicating illness, the participant may be re-assessed for eligibility a minimum of 24 hours later.
2. Female of childbearing potential who has a positive urine pregnancy test within the 24 hours prior to any vaccination or who is currently breastfeeding.
3. Has long-term use (≥14 consecutive days) of glucocorticoids including oral or parenteral prednisone or prednisone equivalent (>20 mg total dose per day) or high-dose inhaled steroids (>800 µg/day of beclomethasone dipropionate or equivalent) within 1 month prior to vaccination. However, participants on low-dose inhaled steroids (≤800 µg/day of beclomethasone dipropionate or equivalent) or topical steroids are not excluded.
4. Has received any (licensed or under EUA) live vaccines within 4 weeks or inactivated, mRNA, or recombinant protein vaccines within 2 weeks of the current visit.
5. Has any laboratory test result or clinical findings (including vital signs) that singly or in combination are likely to unfavorably alter the risks of participant participation or to confound study safety or immunogenicity results, in the opinion of the site investigator. Additionally, the following are exclusionary:
    a. ALT or AST >2 times the ULN, or
    b. Bilirubin >1.5 times the ULN, unless isolated Gilbert's syndrome.
6. Has any disease or medical condition that, in the opinion of the site investigator, might confound interpretation of safety or immunogenicity.

8.2. Participant Withdrawal

8.2.1. Participant Withdrawal Criteria

Every participant has the right to refuse participation in the study (i.e., withdraw consent) at any time without providing any reason for withdrawal. A participant's participation must be terminated immediately upon his/her request, and the reason(s) for discontinuation documented accordingly in the corresponding electronic Case Report Form (eCRF).

Any participant who meets one or more of the following criteria will be removed from the study without prejudice:

- Participant request.
- Participant noncompliance, defined as refusal or inability to adhere to the study protocol or any other instances determined by the site investigator or BARDA.
- Participant lost to follow-up.
- Site investigator no longer believes participation is in the best interest of the participant.
- At request of BARDA, regulatory agencies, or the IRB

For any participant who meets the above criteria, the Early Termination (ET) Visit assessments should be performed as outlined in the Schedule of Assessments (Appendix 1), when possible. If a participant has a diary in their possession at the ET Visit, the diary should be reviewed and collected. If the participant is willing, a new diary should be issued if the schedule requires that they still fill out a diary. If the ET Visit occurs within 7 days after either of the 2 study vaccinations, an injection site assessment should be performed.

If it is not possible to conduct the ET Visit, site staff should make every effort to collect AE, SAE, MAAE, and pIMD information by phone.

8.2.2. Replacements

If a participant is withdrawn from the clinical trial after receipt of the first dose of vaccine, the participant will not be replaced.

If a participant is randomized but does not receive the first dose of vaccine, the participant will be withdrawn and will not be counted toward the total enrollment goal. Additional participants will be randomized to achieve enrollment goals.

9. TREATMENT OF PARTICIPANTS

9.1. Description of Study Vaccine Antigens and Adjuvants

A summary of the study vaccine antigens and adjuvants to be evaluated in this study is presented in Table 5. The study vaccines will be prepared for IM injection by mixing an egg-based antigen with AS03A full dose, AS03A half dose (H5N8 only), or MF59 as follows:

- H5N8 vaccine
  - Antigen mixed 1:1 with AS03A adjuvant for groups receiving a full dose of AS03A.
  - Antigen mixed 1:0.5 with AS03A adjuvant for groups receiving a half dose of AS03A.
  - Antigen mixed 1:1 with MF59 adjuvant.
- H5N1 vaccine
  - Antigen mixed 1:1 with AS03A adjuvant for the groups receiving a full dose of AS03A and 3.75 or 7.5 µg H5N1.
  - Antigen mixed 1:1 with MF59 adjuvant for the groups receiving 3.75 or 7.5 µg H5N1.
  - Antigen mixed 1:0.5 with AS03A adjuvant for the groups receiving a full dose of AS03A and 15 µg H5N1.
  - Antigen mixed 1:0.5 with MF59 adjuvant for the groups receiving 15 µg H5N1.

Study vaccine will be administered by an unblinded study staff member in a volume of 0.375 mL, 0.5 mL, or 0.75 mL, depending on the treatment group of the participant.

Table 5: Summary of Study Vaccine Antigens and Adjuvants

Product Name	Manufacturer	Concentrations	Physical Description
Egg-A/Astrakhan/3212/2020 (H5N8)	Sanofi	15 µg/mL 30 µg/mL 60 µg/mL	Slightly opalescent suspension
Egg-A/bar-headed goose/Qinghai Lake/1A/2005 (H5N1)	Sanofi	15 µg/mL 30 µg/mL	Slightly opalescent suspension
AS03A	GSK	41.5 mg squalene/mL	Milky white oil-in-water emulsion
MF59	CSL Seqirus	38 mg squalene/mL	Milky white oil-in-water emulsion

9.1.1. Description of Study Vaccine Antigens

9.1.1.1. Egg-A/Astrakhan/3212/2020 (H5N8)

Influenza virus Egg-A/Astrakhan/3212/2020 (H5N8) vaccine, a monovalent type A inactivated vaccine for IM use, is a sterile suspension prepared from pandemic influenza virus candidate vaccine propagated in embryonated chicken eggs.

The vaccine contains thimerosal. The final product is clear and slightly opalescent in color. The Egg-A/Astrakhan/3212/2020 (H5N8) vaccine antigen will be supplied in vials intended for single use at antigen concentrations that, following mixing with adjuvant, will yield an antigen dose of 3.75, 7.5, or 15 µg delivered by IM injection. Specific details regarding study vaccine mixing and administration will be defined in the pharmacy manual.

9.1.1.2. Egg-A/bar-headed goose/Qinghai Lake/1A/2005 (H5N1)

Influenza virus Egg-A/bar-headed goose/Qinghai Lake/1A/2005 (H5N1) vaccine, a monovalent type A inactivated vaccine for IM use, is a sterile suspension prepared from pandemic influenza virus candidate vaccine propagated in embryonated chicken eggs.

The final product is clear and slightly opalescent in appearance. The Egg-A/bar-headed goose/Qinghai Lake/1A/2005 (H5N1) vaccine antigen will be supplied in vials at antigen concentrations that, following mixing with adjuvant, will yield an antigen dose of 3.75, 7.5, or 15 µg delivered by IM injection. Specific details regarding study vaccine mixing and administration will be defined in the pharmacy manual.

9.1.2. Description of Study Vaccine Adjuvants

9.1.2.1. AS03A

The AS03A adjuvant is an oil-in-water emulsion containing DL-α-tocopherol, squalene, polysorbate 80, and a buffer. A full dose of AS03A is 0.25 mL and is milky white in appearance. Refer to Table 6 for the composition details.

Table 6: AS03A Adjuvant Composition

Component	Quantity per mL or [Concentration]
Squalene	[redacted]
α-tocopherol	[redacted]
Polysorbate 80	[redacted]
Sodium chloride	[redacted]
Potassium chloride	[redacted]
Disodium phosphate anhydrous	[redacted]
Potassium dihydrogen phosphate	[redacted]
Water for injection	[redacted]

9.1.2.2. MF59

The MF59 adjuvant is an oil-in-water emulsion composed of squalene, stabilized by the addition of two emulsifiers, polysorbate 80 and sorbitan trioleate (Span 51), and a low ionic strength buffer. The MF59 adjuvant is milky white in appearance. Refer to Table 7 for the composition details.

Table 7: MF59 Adjuvant Composition

Component	Quantity per mL
Squalene	[redacted]
Polysorbate 80	[redacted]
Sorbitan trioleate	[redacted]
Sodium citrate, dihydrate	[redacted]
Citric acid, monohydrate	[redacted]
Water for injection	[redacted]

9.2. Concomitant Medications and Therapies

Any medication, including all prescription drugs, vaccines, herbal products, vitamins, minerals, and over-the-counter (OTC) medications administered from the time of consent through the end of study participation, is considered a concomitant medication. Concomitant medication use will be recorded and will include the medication name, dose, frequency, route of administration, and the dates of administration. Concomitant therapies will also be recorded. Any changes, additions, and/or deletions in concomitant medications or therapies will be recorded throughout the course of the participant's participation in the study.

If it is discovered that a participant is using a prohibited concomitant medication or therapy after he or she is enrolled in the study, the site investigator, in consultation with the medical monitor

in cases of uncertainty, should determine the impact on the participant's participation. All instances of use of prohibited concomitant medications or therapies must be documented.

In addition, any vaccines received within 90 days prior to the Screening Visit will be recorded.

9.2.1. Prohibited Concomitant Medications and Therapies

The following concomitant medications and therapies are prohibited for the duration of the study unless otherwise specified.

- Anticancer chemotherapy (cytotoxic) or radiation therapy.
- Long-term use (≥14 consecutive days) of glucocorticoids, including oral or parenteral prednisone or prednisone equivalent at a dose of ≥20 mg daily.
- High-dose inhaled corticosteroids (>800 µg/day of beclomethasone dipropionate or equivalent).
- Treatment with immunoglobulin or other blood products.
- Any vaccine (licensed or available under EUA), including live vaccines, inactivated vaccines, mRNA vaccines, and recombinant protein vaccines (including seasonal influenza vaccines and COVID-19 vaccines) from screening through 22 days following the second dose of study vaccine, inclusive of the vaccination day (Screening Visit through Visit 5 [Day 43]).
- Investigational agents (vaccine, drug, biologic, device, blood product, or medication).

9.2.2. Permitted Concomitant Medications and Therapies

Other than the prohibited medications and therapies listed in Section 9.2.1, treatment with concomitant medications and therapies is permitted during the study. Non-study vaccines (including seasonal influenza vaccines) are permitted only beginning 22 days following the second dose of study vaccine, inclusive of the vaccination day (i.e., after Visit 5 [Day 43]). Concomitant medication deemed necessary for the welfare of the participant during the study may be given at the discretion of the site investigator. However, it is the responsibility of the site investigator to ensure that details regarding the medication are recorded in full.

9.3. Treatment Compliance

The study vaccine will be administered by an unblinded study staff member and thus is an observed compliance. Participant compliance will be determined by the number and percentage of participants who receive the entire dose of study vaccine at Visit 1 (Day 1) and Visit 3 (Day 22) by treatment group. Any deviations from the dosing schedule outside the defined visit windows (Appendix 1) must be approved by the BARDA Medical Officer and will be recorded.

10. STUDY VACCINE MATERIALS AND MANAGEMENT

10.1. Study Vaccine

Study vaccines will be supplied as 2 components (antigen and adjuvant) that must be mixed prior to administration. Refer to Section 9.1 for detailed information regarding mixing ratios, study vaccine antigens, and study vaccine adjuvants.

10.2. Study Vaccine Packaging and Labeling

Study vaccines will be packaged and labeled according to applicable local and regulatory requirements. Study vaccine will be provided in single-dose kits containing 1 vial of antigen and 1 vial of adjuvant. Vials will be labeled with a single-panel, unblinded label.

The vials and kits will be labeled in English. The vial and kit labels will include the Sponsor Name (BARDA), protocol number, and a note that specifies the following, “Caution: New Drug – Limited by Federal Law to Investigational Use Only”, as well as storage specifications. In addition, the vial labels will contain the antigen or adjuvant lot number.

10.3. Study Vaccine Storage

Study vaccine kits containing antigen and adjuvant must be stored in a secure area (e.g., a locked room or locked refrigerator), protected from light and moisture, and kept at a controlled standard refrigeration temperature between 2°C to 8°C (36° to 46°F), inclusive. The temperature of the storage unit must be monitored, and documentation of proper storage must be maintained. Vaccine components should be removed from the refrigerated storage unit and allowed to warm to room temperature for approximately 15 minutes before mixing.

10.4. Study Vaccine Preparation and Administration

Antigen and adjuvant will be mixed prior to administration according to the details outlined in the Manual of Procedures (MOP). Mixing ratios of antigen and adjuvant are described in Section 9.1. The vaccine once mixed should have a milky white appearance. The vaccine should be visually inspected for particulate matter and discoloration prior to administration; it should not be administered if either condition exists.

The vaccine must be administered by IM injection in the deltoid muscle of the arm within 30 minutes of mixing. Each vaccination will be given in a different arm, unless a skin condition prevents administration in one of the arms (e.g., scar tissue, skin rash, etc.). The vaccine administrator will record which arm received the injection.

10.5. Study Vaccine Accountability

The site investigator is required to maintain adequate records of the disposition of the study vaccine, including the date and quantity of vaccine received, to whom the vaccine was dispensed (participant-by-participant accounting), and a detailed accounting of any vaccine accidentally or deliberately destroyed. Records for receipt, storage, use, and disposition will be maintained by the study site. A vaccine dispensing log will be kept current and will include kit IDs, identification of each participant, and the date and quantity of vaccine dispensed. All records

regarding the disposition of the study product will be available for inspection by the unblinded study monitor.

10.6. Study Vaccine Handling and Disposal

After dosing has been completed, to satisfy regulatory requirements regarding accountability, all used and unused study vaccine (i.e., antigen and adjuvant) will be reconciled. Study vaccine should not be destroyed until authorized in writing by BARDA. The used and unused study vaccine will be returned to the distributor for disposition per applicable regulations.

10.7. Randomization and Blinding

10.7.1. Randomization

Participants 18 through 64 years old will be randomized equally to 1 of 13 treatment groups (A, B, C, D, E, F, G, H, I, J, K, M, and N), and participants ≥65 years old will be randomized equally to 1 of 10 treatment groups (B, C, E, F, H, I, K, L, N, and O), as specified in Table 3. A web-based randomization system will be used to centrally administer the randomization schedule. The randomization schedule will be computer generated by the coordinating center. Randomization will take place according to a fixed schedule using a permuted block design stratified by age group. Participants will be assigned to treatment groups based on the predefined randomization schedule. The randomization schedule will be generated by the unblinded randomization team and will be kept strictly confidential, accessible only to authorized unblinded persons (Section 10.7.2).

10.7.2. Blinding

This is a double-blind study. The study staff members who will prepare and/or administer the study vaccine will be unblinded to treatment group assignment. The unblinded study staff will not be involved with safety evaluations, nor will they perform subsequent assessments or engage in other study activities that could reveal the blind. Site investigators, all investigational site staff (except those responsible for preparing/administering the vaccine), and all participants participating in this study will be blinded to treatment group assignment. Laboratory staff performing the safety laboratory assessments and immunogenicity assays will be blinded to treatment group.

To preserve the study blind, a minimum number of Rho, ICON plc (ICON), and BARDA personnel will have access to treatment randomization information at the individual participant level. The unblinded Rho study team will include an unblinded statistical team, Rho Client Support Services, and web-based randomization system teams. The unblinded ICON team will include a clinical team lead and study monitor(s). During monitoring visits, the unblinded study monitor(s) will perform study vaccine accountability and will check that the blind has been maintained. Blinded study monitor(s) will continuously assess the progress of the study but will not have access to the unblinded study records. A BARDA representative may be unblinded to assist with oversight of the study vaccine management. In addition, as needed to meet regulatory reporting requirements, designated pharmacovigilance and/or regulatory personnel may be unblinded to the treatment status of individual participants. In this circumstance, and if there are

no other concerns, neither the BARDA project coordination team nor the study staff will be further unblinded to treatment status.

If an SMC meeting is needed (Section 7.4.2), the members of the SMC may review safety data fully unblinded at the treatment group and participant level, as necessary, during the closed session meeting.

10.7.3. Breaking the Blind

Unblinding of individual participants should occur only when knowledge of the treatment assignment will have a direct bearing on the medical treatment or evaluation of a participant. Whenever possible, the need to unblind should be discussed with BARDA and the medical monitor prior to unblinding. In the event of an emergency, the site investigator or designated qualified individual may obtain the participant's blinded treatment via the web-based randomization system. If an individual designated to perform emergency unblinding does not have access to the web-based randomization system, Rho Client Support Services may be contacted and can perform the unblinding for that individual. Upon performance of a blind break within the web-based randomization system, the system will send out a blinded notification to alert Rho and BARDA staff of the event.

A full account of the unblinding event will be recorded in the participant's eCRF, including the date and time of the unblinding, the reason for the decision to unblind, the extent of unblinding, and the name and signature of the individual who made the decision to unblind. The treatment assignment should not be included in the eCRF.

The blinding at the participant level will be maintained to those outside the unblinded team, including all blinded site and laboratory staff, until database lock of all data through the EoS Visit (Visit 6; Day 203).

11. ASSESSMENT OF IMMUNOGENICITY

Venous blood samples will be collected for immunogenicity assays at the Screening Visit, Visit 3 (Day 22) prior to vaccination, Visit 5 (Day 43), and the EoS Visit (Visit 6; Day 203). Serum will be shipped to the central laboratory for storage and subsequently shipped to the immunogenicity laboratory for analysis. Good Clinical Laboratory Practice (GCLP)-compliant HAI and MN assays will be conducted to determine titers of HAI and MN antibodies, respectively. Good Laboratory Practice will be conducted while ensuring that the integrity and reliability of data satisfy GCLP requirements consistent with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines (e.g., documented quality control (QC)/quality assurance (QA), protection of patient confidentiality, etc).

The details for sample handling, processing, and shipping will be provided in the MOP.

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

Safety will be evaluated utilizing the assessments defined in this section. If deemed clinically necessary, additional safety assessments not currently specified in the protocol may be performed at the discretion of the site investigator in consultation with the medical monitor and BARDA.

12.1.1. Demographic/Medical History

To define a baseline for potential AEs, the demographics and medical history of each participant will be collected at the Screening Visit.

12.1.2. Vital Signs

Vital sign measurements, including oral temperature, pulse rate, respiratory rate, and diastolic and systolic blood pressure, will be collected at Screening, Visit 1 (Day 1), Visit 3 (Day 22), and Visit 5 (Day 43). Vital signs will also be collected at the ET visit, and at an Unscheduled Visit if clinically indicated by the site investigator in consultation with the medical monitor.

Vital signs should be measured before blood is collected. At visits during which study vaccine is administered, vital signs will be taken both pre-vaccination and 30 ± 5 minutes post-vaccination prior to discharge. Respiratory rate, if regular, may be assessed over 30 seconds and doubled, but in no case should it be assessed over a period of less than 30 seconds. Pulse rate assessment, if performed manually, must be assessed over at least 15 seconds.

Prior to the second vaccination (Visit 3, Day 22), if the participant's oral temperature is above 100.4°F, indicating illness, the participant may be re-assessed for eligibility a minimum of 24 hours later.

Participants will also self-assess oral temperature as part of the diary process, described in more detail in Section 12.1.6.

12.1.3. Weight and Height

Participant's height and weight will be assessed at the Screening Visit. Body mass index (BMI) will be derived automatically from height and weight measurements in the electronic data capture system.

12.1.4. Physical Examination

A full physical examination will be performed at the Screening Visit to assess eligibility and at Visit 3 (Day 22) prior to vaccination. The examination will include a general assessment of the skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, cardiovascular system, abdomen, lymph nodes, musculoskeletal system/extremities, and a neurological examination.

A targeted physical examination will be performed at Visit 1 (Day 1). Additional targeted physical examinations may be performed at all other visits (including an ET or Unscheduled Visit) at which a full physical examination is not scheduled if clinically indicated based on review of interim health status and/or clinical laboratory assessments. The targeted physical

exam will include assessments of the following body systems: skin, ears, nose, throat, lungs, cardiovascular, and musculoskeletal. Additional body systems may also be examined based on reporting of any symptoms or complaints by the participant.

12.1.5. Laboratory Assessments

Venous samples will be obtained for chemistry, complete blood count (CBC) with differential, and coagulation at the Screening Visit, Visit 2 (Day 8), and Visit 4 (Day 29). Samples will also be collected at an ET or Unscheduled Visit if clinically indicated by the site investigator in consultation with the medical monitor. The details for sample handling, processing, and shipping will be provided in the MOP.

The clinical laboratory assessments planned for this study include chemistry and hematology assessments described in more detail below (Section 12.1.5.1 and Section 12.1.5.2).

12.1.5.1. Chemistry

The clinical chemistry assessments planned for this study are listed in Table 8. Participants should fast for at least 8 hours prior to the screening blood work. Participants who have an increased screening AST, ALT, or total bilirubin level, between the ULN and 2-fold the ULN, should be advised to have follow-up with their primary care healthcare provider.

Table 8: Clinical Chemistry Assessments

Alanine aminotransferase	Chloride
Albumin	Creatinine
Alkaline phosphatase	Glucose (random, serum)
Aspartate aminotransferase	Potassium
Bicarbonate	Sodium
Blood urea nitrogen	Total Bilirubin
Calcium	Total Protein

12.1.5.2. Hematology

The hematology assessments planned for this study are listed below:

- Coagulation: partial thromboplastin time and prothrombin time (international normalized ratio)
- CBC with differential; Table 9 lists the parameters of the CBC with differential.

Table 9: Complete Blood Count with Differential

Red blood cells	**White blood cells**
Hematocrit	Basophils (% and absolute count)
Hemoglobin	Eosinophils (% and absolute count)
Red blood cell count	Lymphocytes (% and absolute count)
Platelets	Monocytes (% and absolute count)
Platelet count	Neutrophils (% and absolute count)
	White blood cell count

12.1.5.3. Virus Serology

No blood samples will be collected for virus serology. Participant information regarding human immunodeficiency virus, hepatitis B, and hepatitis C infection will be based on participant medical history.

12.1.5.4. Pregnancy Screen

At the Screening Visit, Visit 1 (Day 1), and Visit 3 (Day 22), a urine pregnancy test will be performed onsite for female participants of childbearing potential. For Visits 1 and 3, the test must be performed within 24 hours prior to vaccination, and results must be final and negative prior to vaccination.

Additionally, a urine pregnancy test should be performed at any time during study participation if pregnancy is suspected.

12.1.6. Participant Diaries

All participants will be provided with access to diaries to aid in their recording of solicited local and systemic reactions through 8 days after each vaccination, inclusive of the vaccination day, and all unsolicited symptoms/complaints through Day 43. Participants will be instructed to fill in the diary at the same time each day to capture observations for the prior 24-hour period.

Participants will also self-assess oral temperature and the dimensions of injection site reactions as part of the diaries. Participant diaries will include instructions, and thermometers and measuring tools (rulers) will be provided to participants and will be replenished as needed. Sites will train each participant on diary completion at Visit 1 (Day 1).

The site investigator or his/her designee will review the information from participant diaries or from memory with the participant at each applicable visit and assess whether any AE criteria are met based on FDA's standard toxicity grading scales (Section 12.3.3). Should any abnormal findings not be resolved when the diary is collected, these events will be followed per Section 12.3.2 during follow-up AE assessments.

12.1.7. Adverse Event Assessment

At all in-person visits, including an ET or Unscheduled Visit, site staff will ask nonleading questions regarding the participant's health status (Section 12.3.1) and document any new or

changed AEs. At Visit 1 (Day 1), AEs will be recorded during the immediate 30-minute observation period following study vaccination. At Visit 3 (Day 22), AEs will be recorded separately prior to vaccination and during the immediate 30-minute observation period following study vaccination. If a participant discontinued and declines to participate in an onsite ET Visit, study staff should attempt to collect AE information by phone.

12.1.8. Concomitant Medications and Therapies Assessment

All medications and therapies the participant is receiving at the time of the Screening Visit and any vaccines received within 90 days prior to the Screening Visit will be recorded in the participant's eCRF. Site staff will review concomitant medications and therapies (Section 9.2) at Visit 1 and all subsequent visits, including an ET or Unscheduled Visit. Changes in medications, therapies, and any vaccinations received since the last visit will be recorded at subsequent visits.

On days at which study vaccine is to be administered (Visit 1 [Day 1] and Visit 3 [Day 22]), concomitant medications and therapies should be recorded prior to vaccination.

12.1.9. Injection Site Evaluation

Injection site evaluations will be performed to assess injection site erythema/redness, induration/swelling, and pain. On study vaccination days (Visit 1 [Day 1] and Visit 3 [Day 22]), the injection site will be examined 30 ±5 minutes after injection. The injection site will be assessed again at the visit following each study vaccination (Visit 2 [Day 8] and Visit 4 [Day 29]). The injection site will also be assessed at an ET or Unscheduled Visit if that Visit occurs within 7 days after either of the 2 study vaccinations.

If a visible injection site abnormality is observed, the area (largest diameter) of erythema/redness and/or induration/swelling will be measured and documented.

12.1.10. Post-vaccination Evaluation

At Visit 1 (Day 1) and Visit 3 (Day 22), participants will be monitored for at least 30 minutes after vaccination.

The following evaluations will also be performed:

1. Vital signs assessment (Section 12.1.2)
2. Injection site evaluation (Section 12.1.9)

During this period, any solicited and unsolicited TEAEs, SAEs, and MAAEs will be recorded, as well as any concomitant medications taken for these events.

12.2. Adverse and Serious Adverse Events

12.2.1. Definition of Adverse Events

12.2.1.1. Adverse Event (AE)

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not it is considered drug related [21 Code of Federal Regulations [CFR] 312.32(a)].

Laboratory results and vital sign excursions of any magnitude will be defined as AEs if they are considered clinically significant by the site investigator. A lab or vital sign result should generally be considered clinically significant and an AE if, regardless of degree out of range, it has a reasonable probability of reflecting or contributing to a disturbance of homeostasis or pathological process or outcome.

Suspected adverse reaction (SAR) means any AE for which there is a reasonable possibility that the drug caused the event. For the purposes of safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. A SAR implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug [21 CFR 312.32(a)].

An AE or SAR is considered "unexpected" if it is not listed in the investigator brochures for Egg-A/Astrakhan/3212/2020 (H5N8), Egg-A/bar-headed goose/Qinghai Lake/1A/2005 (H5N1), AS03A, or MF59 or is not listed at the specificity or severity that has been observed.

12.2.1.2. Solicited and Unsolicited Adverse Events

For the purposes of this study, the following specific local and systemic AEs will be solicited from the participant for 8 days post-vaccination, inclusive of the vaccination day (Day 1 through Day 8 and Day 22 through Day 29):

- Solicited local reactions at the injection site will include erythema/redness, induration (underlying hardening of tissue associated with inflammation)/swelling (localized tissue distension), and pain.
- Solicited systemic reactions will include fever, myalgia, arthralgia, fatigue, headache, nausea, vomiting, diarrhea, and chills.

All other AEs reported by the participant will be defined as unsolicited AEs. All unsolicited TEAEs through Day 43 will be recorded. After Day 43, unsolicited AEs will be recorded only if they are defined as SAEs, MAAEs, or pIMDs (Section 12.3.2 and Figure 2).

12.2.1.3. Serious Adverse Event (SAE)

An AE or SAR is considered "serious" if, in the view of either the site investigator or BARDA, it results in any of the following outcomes [21 CFR 312.32(a)]:

- Death
- Life-threatening adverse event that in the view of the site investigator or BARDA, places the participant at immediate risk of death. This does not, however, include an event that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongs existing hospitalization. Planned hospitalizations will not be reported as SAEs unless categorized as medically important. Emergency room visits and observational admissions of under 24 hours, in themselves, do not qualify as SAEs.
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly/birth defect.

- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience, when based on appropriate medical judgment, they may jeopardize the participant or the participant may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

12.2.1.4. Medically Attended Adverse Events

Some adjuvants, including AS03A and MF59, are used in vaccine formulations because they are potent inducers of the immune system. Out of an abundance of caution, MAAEs reported for participants in all treatment groups from the time of the first vaccination through the EoS Visit (Visit 6; Day 203) will be collected and analyzed due to the theoretical potential for induction of autoimmune or autoinflammatory diseases.

Medically attended adverse events are defined as AEs with medically attended visits including hospital, emergency room, urgent care clinic, or other visits to or from medical personnel for any reason. Adverse events (e.g., abnormal vitals) identified at a routine study visit will not be considered MAAEs.

12.2.1.5. Potentially Immune-Mediated Diseases

Some adjuvants, including AS03A and MF59, are used in vaccine formulations because they are potent inducers of the immune system. Out of an abundance of caution, pIMDs reported for participants in all treatment groups from the time of the first vaccination through the end of study will be collected and analyzed due to the theoretical potential for induction of autoimmune or autoinflammatory diseases.

For this study, the occurrence of a pIMD is considered to be unexpected and will be reported as a SUSAR per 21 CFR 312.32.

A list of pIMDs defined for this study is presented in Appendix 3.

12.3. Collection, Recording, and Grading Severity of Adverse Events

12.3.1. Collection of Adverse Events

Adverse events of any type described above may be discovered through a variety of methods:

- Observing the participant.
- Reviewing and discussing the diary data with the participant (Section 12.1.6).
- Questioning the participant with standard nonleading questions to elicit any medically related changes in their well-being (Have you been hospitalized, had any accidents, used any new medications, or changed any medications [both prescription and OTC]?).
- Receiving an unsolicited complaint from the participant.
- An abnormal value or result from a clinical (e.g., vital signs) or laboratory evaluation.

12.3.2. Recording Adverse Events

The site investigator will record AEs. Only treatment-emergent AEs (i.e., those occurring from the time the participant receives the first vaccination until exit from the study) will be recorded.

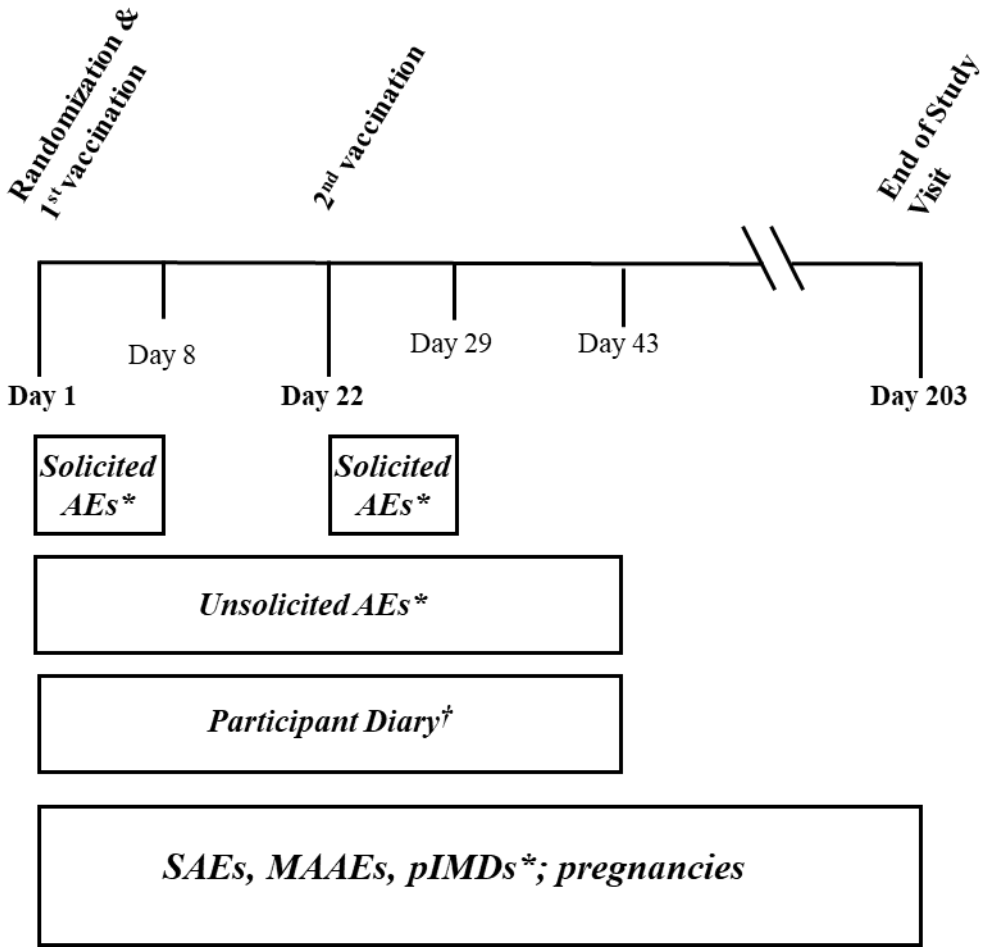
Any clinically significant safety assessments that are associated with an underlying disease present at screening, unless judged by the site investigator to be more severe than expected for the participant's condition, are **not** to be reported as AEs or SAEs. Due to expectedness of mild fever and mild redness and swelling at the injection site, any symptoms of erythema/redness, induration/swelling and fever that do not meet the Grade 1 lower thresholds in Appendix 2 are **not** to be reported as AEs.

For all AEs, those judged related to study vaccine will be followed to resolution (with or without sequelae) or until considered stable by the site investigator (in consultation with the medical monitor in situations of uncertainty). Those judged unrelated to study vaccine will be followed to resolution (with or without sequelae) or, if not resolving, until considered stable by the site investigator (in consultation with the medical monitor in situations of uncertainty), or until the end of the participant's study participation, whichever comes first. Adverse events will be recorded during the periods defined below.

- Solicited AEs:
  - Those occurring with onset within 8 days following each vaccination, inclusive of the vaccination day (Day 1 through Day 8 and Day 22 through Day 29).
- Unsolicited AEs
  - All AEs other than solicited local and systemic reactogenicity symptoms with onset within 22 days following each vaccination, inclusive of the vaccination day (Day 1 through Day 22 and Day 22 through Day 43). Outside of these specified windows, unsolicited AEs will only be recorded if they are defined as SAEs, MAAEs, or pIMDs.
- SAEs, MAAEs, and pIMDs:
  - Those occurring from the time the participant receives the first vaccination until exit from the study.
  - SAEs and pIMDs will be reported to Rho pharmacovigilance personnel within 1 business day of the site's awareness of the event via entry into the electronic data capture (EDC) system. Only MAAEs meeting SAE criteria must be reported within 1 business day.

Figure 2 provides the safety data reporting periods used in this study.

Figure 2: Safety Data Reporting Periods



AE = adverse event; SAE = serious adverse event; MAAE = medically attended adverse event; pIMD = potentially immune-mediated diseases
* Only treatment-emergent AEs (i.e., those occurring from the time the participant receives the first vaccination until exit from the study) will be collected during this study.
† Participants will be instructed to record solicited local and systemic reactions through 8 days after each vaccination, inclusive of the vaccination day, and all unsolicited symptoms/complaints through Day 43. Any abnormal findings will be followed per Section 12.3.2 during follow-up AE assessments.

12.3.3. Grading Severity of Adverse Events

The severity of AEs and SAEs will be graded as defined by the FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (2007, Appendix 2).[19] For unsolicited TEAEs that are not included in Appendix 2, the severity grading will be based upon the participant's individual assessment of the extent to which the AE interfered with their regular daily activities as follows:

- Grade 0 (Absent) = symptom not present.
- Grade 1 (Mild) = symptom present but does not interfere with activities of daily living.

- Grade 2 (Moderate) = symptom causes some interference with activities of daily living.
- Grade 3 (Severe) = symptom prevents activities of daily living or requires treatment.
- Grade 4 (Potentially Life Threatening) = symptom requires emergency room visit or hospitalization.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity, whereas seriousness is defined by the criteria in Section 12.2.1.3.

12.4. Relationship and Attribution to Study Vaccine

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the study product caused or contributed to an AE and must be provided for all AEs (serious and non-serious). The site investigator will assess the causality/relationship between the study product and the AE and record that assessment in the appropriate eCRF.

BARDA's determination of attribution will be used for reporting to the appropriate health and regulatory authorities.

The relation and attribution of an AE to study product will be determined using the descriptors and definitions provided in Table 10.

Table 10: Attribution of Adverse Events

Unrelated Categories	
Not Related	The AE is clearly not related to vaccination.
Unlikely Related	The AE is unlikely related to vaccination.
Related categories	
Possibly Related	The AE has a reasonable possibility to be related to vaccination; there is evidence to suggest a causal relationship.
Probably Related	The AE is likely related to vaccination.
Related	The AE is clearly related to vaccination.

AE = adverse event

12.5. Reporting Safety Events to Regulatory Authorities

Once AEs, SAEs, MAAEs and pIMDs are recorded, Rho pharmacovigilance personnel will collaborate with BARDA and appropriate personnel to process and report events to the appropriate regulatory authorities within applicable regulatory timeframes. Procedures for AE processing and reporting are detailed in the Data Safety Monitoring Plan (DSMP).

The sponsor will report any SUSAR to the FDA. Potentially immune-mediated diseases (Appendix 3) will be submitted as SUSARs.

The sponsor will report an AE as a SAR only if there is evidence to suggest a causal relationship between the study vaccine and the adverse event, such as:

a. A single occurrence of an event that is uncommon and known to be strongly associated with vaccine exposure (e.g., angioedema, Stevens-Johnson syndrome, Guillain-Barré syndrome);
b. One or more occurrences of an event that is not commonly associated with vaccine exposure, but is otherwise uncommon in the population exposed to the study product e.g., narcolepsy);
c. An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of treatment) that indicates those events occur more frequently in the treatment group than in a concurrent or historical control group (21CFR 312.32(a)).
d. Potentially immune-mediated diseases (Appendix 3) will be submitted as SUSARs.

12.6. Pregnancy Reporting

This study includes pregnancy as safety data. Although pregnancy is not an SAE, information about any pregnancy in a female study participant should be reported to Rho pharmacovigilance personnel within 1 business day of the site's awareness of the event for tracking purposes.

Vaccine administration will be discontinued for the pregnant participant. The site investigator shall counsel the pregnant participant and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the pregnant participant shall continue until the conclusion of the pregnancy.

The pregnancy will be documented when identified and at its conclusion.

Should pregnancy result in a congenital abnormality, birth defect, miscarriage, or medically indicated abortion, an SAE must be submitted to Rho using the SAE reporting procedures described in Section 12.3.2.

If pregnancy is ongoing at study conclusion, the site investigator will report the outcome of the pregnancy to BARDA.

12.7. Reporting Other Safety Information

Site investigators should promptly notify Rho, ICON, BARDA, and the IRB when an unanticipated problem involving risks to participants or others, which is not otherwise reportable as an AE, is identified.

13. STATISTICS

13.1. Endpoints

Endpoints are summarized in Table 2 under Section 6.

Definitions of seroprotection and seroconversion included in the endpoints are provided below:

- Seroprotection based on serum HAI antibody titers: defined as an HAI antibody titer ≥1:40
- Seroconversion based on serum HAI antibody titers: defined as either a pre-vaccination HAI titer <1:10 and a post-vaccination HAI titer ≥1:40, or a pre-vaccination HAI titer ≥1:10 and a minimum 4-fold rise in post-vaccination HAI titer
- Seroconversion based on serum MN antibody titers: defined as either a pre-vaccination MN titer <1:10 and a post-vaccination MN titer ≥1:40, or a pre-vaccination MN titer ≥1:10 and a minimum 4-fold rise in post-vaccination MN titer

13.1.1. Measures to Minimize Bias

Stratified permuted block randomization will be performed centrally and will balance randomization between treatment groups within each age group (see Section 10.7.1 for more details). Clinical staff observing the participant following vaccine administration, laboratory personnel analyzing samples, and study participants will be blinded to treatment group (Section 10.7.2). Site staff will be trained in procedures to ensure blinding is maintained for all blinded individuals.

An independent unblinded statistical team (Section 10.7.2) will generate, interpret, and report each analysis using appropriate treatment groups and will not modify any programs used to perform analyses.

13.1.2. Analysis Plan

Due to the exploratory nature of the study objectives, no formal hypothesis testing is planned. Descriptive statistics (e.g., percentages for categorical data and means, standard deviations, geometric means [for immunogenicity data only], medians, quartiles, and ranges for continuous data) will be used to summarize participant characteristics and safety and immunogenicity endpoints. These summaries will be presented overall and separately for the treatment groups, as appropriate. Summaries will also be presented for pooled groups by antigen, antigen dose level and by adjuvant, as appropriate. Details of the statistical analyses, methods, and data conventions will be described in the Statistical Analysis Plan (SAP).

13.1.2.1. Analysis Populations

13.1.2.1.1. Safety Population

The safety population will include all participants who are randomized and receive at least one vaccination. For individual safety summaries of each vaccine dose, each participant will be analyzed as part of the treatment group corresponding to the actual treatment received for the applicable vaccine dose. For all other safety analyses by group, each participant will be analyzed

corresponding to the actual treatment received for their vaccine dose. The safety population will be used for all safety analyses.

13.1.2.1.2. Immunogenicity Full Analysis Population

The immunogenicity full analysis population (IFAP) will include all participants who are randomized, receive at least one vaccination, and have determinate assay results at any post-vaccination visit. Each participant will be analyzed as part of the treatment group assigned by randomization, regardless of the treatment actually received. All immunogenicity analyses will be performed on the IFAP.

13.1.2.1.3. Immunogenicity Per Protocol Population

The immunogenicity per protocol population (IPPP) will include all participants who meet the following criteria:

- Are in the IFAP.
- Received a full dose of vaccine at Day 1 and a full dose of vaccine at Day 22 (Appendix 1).
- Received the correct treatment as assigned by randomization.
- Have no other major protocol deviations that may have an impact on immunogenicity assessments.
- Have determinate assay results at the Day 43 visit.

All immunogenicity analyses will also be performed on the IPPP.

13.1.2.2. Primary Analysis

13.1.2.2.1. Primary Safety Analyses

The number and percentage of participants experiencing solicited local reactogenicity symptoms, as defined in Section 12.2.1.2, will be summarized by system organ class and preferred term. The total number of events in each treatment group will be reported. The rate and corresponding 95% CI of events in each treatment group may also be reported. Solicited systemic reactogenicity symptoms will be summarized in a similar manner. Events will be included in the primary safety endpoints only if they occur within 8 days of each vaccination, inclusive of the vaccination day (Day 1 through Day 8 and Day 22 through Day 29).

13.1.2.2.2. Primary Immunogenicity Analyses

The percentage of participants achieving seroprotection at Day 43 based on serum HAI antibody titers to A/Astrakhan (H5N8) and the corresponding 95% CI will be reported for each treatment group.

13.1.2.3. Secondary Analyses

The 4 secondary safety endpoints (Table 2) will be summarized in the same manner as the primary safety endpoints. Additionally, the primary and secondary safety endpoints will be

summarized by vaccination (i.e., Dose 1 or Dose 2), onset days following each vaccination, grade, duration, and relationship to the study vaccine.

HAI and MN antibody titers to A/Astrakhan (H5N8) and A/bar-headed goose (H5N1) will be summarized as GMT by treatment group at Screening and Days 22, 43, and 203 with the corresponding 95% CIs about the GMT for each group.

Secondary immunogenicity endpoints related to seroprotection and seroconversion will be summarized in the same manner as the primary immunogenicity endpoint. The percentage of participants achieving seroprotection based on serum HAI antibody titers to A/bar-headed goose (H5N1) will be summarized at Day 43. The percentage of participants achieving seroprotection based on serum HAI antibody titers to A/Astrakhan (H5N8) and A/bar-headed goose (H5N1) will be summarized at Days 22 and 203. For both A/Astrakhan (H5N8) and A/bar-headed goose (H5N1), the percentage of participants achieving seroconversion based on serum HAI antibody titers and serum MN antibody titers will be summarized at Days 22, 43, and 203. Definitions of seroprotection and seroconversion can be found in Section 13.1.

Additional information regarding listings and tabular summaries of safety assessments and immunogenicity measures will be specified in the SAP.

13.1.2.4. Interim Analysis

An interim analysis will be performed based on available cumulative immunogenicity and safety data through Day 43 for all participants. At the time of the interim analysis, the study database (all available data through Day 43) will be monitored and cleaned per the associated study plans. The unblinded Day 43 analysis will be compiled by an unblinded statistical team, and data from the interim analysis will be aggregated at the group level; thus, participant-level blinding will be maintained for those outside of the unblinded team until database lock of all data through the end of study. Available primary and secondary endpoints through Day 43 will be summarized for the interim analysis. No decisions regarding the status of the study will be made as a result of the interim analysis, and there will be no penalty for an early look at the data. Further details will be specified in the SAP.

13.1.2.5. Ad Hoc SMC Meeting

There are no formal or planned SMC meetings. An SMC review will only occur when 1 or more of the findings leading to study suspension are met and for any immediate safety concerns observed. Data displays for any SMC review will be generated by the appropriate blinded or unblinded statistical team. The operations of the SMC will be specified in the SMC charter.

13.1.2.6. Final Analysis

The final analyses will include all safety and immunogenicity data through the EoS Visit (Visit 6; Day 203; Appendix 1). The study database will be monitored, cleaned, and locked per the associated study plans. Study data will be unblinded to prepare the final analyses. Cumulative summaries of all SAEs, MAAEs, and pIMDs occurring from Day 1 through the end of study will be included. Further details will be specified in the SAP.

13.2. Sample Size Considerations

No formal power analyses were conducted since the study objectives require no formal hypothesis testing. The sample size for this study is approximately 1380 participants, including 780 participants 18 through 64 years old who will be randomized equally to 1 of 13 treatment groups (A, B, C, D, E, F, G, H, I, J, K, M, and N) and 600 participants ≥65 years old who will be randomized equally to 1 of 10 treatment groups (B, C, E, F, H, I, K, L, N, and O), as defined in Table 3 in Section 7.3. The proposed sample size for this study is based on previous experience with similar influenza vaccine studies. The previous studies had study arms of similar size that proved to be sufficient to allow the collection of meaningful data, especially with respect to local and systemic reactogenicity symptoms and antibody levels.[20-22]

Though no formal hypothesis testing will be performed as part of the primary analyses, Table 11 and Table 12 show the probability of observing a safety event and statistical power to detect crossing a threshold in seroprotection rate, respectively, under a variety of hypothetical scenarios. Within each table, separate calculations are performed for selected group sample sizes of interest.

Probabilities of detecting at least one safety event were calculated using the binomial distribution (Table 11).

Table 11: Probability of Observing at Least One Safety Event of Interest Under Different True Event Rates

True Probability of a Safety Event	Group Sample Size		
	N=60	N=120	N=180
0.005	0.260	0.452	0.594
0.01	0.453	0.701	0.836
0.02	0.702	0.911	0.974
0.05	0.954	0.998	>0.999
0.1	0.998	>0.999	>0.999

Lower bounds of 70% and 60% are considered to be meaningful thresholds of success for the seroprotection rate for influenza vaccines for ages 18-64 and ≥65 years old, respectively.[23,24] Assuming a one-sided alpha level of 0.025, an exact binomial test was used to calculate the power to detect the lower bound of an exact 95% CI about an observed seroprotection rate being ≥70% or ≥60%, using group sample size and hypothetical true seroprotection rate scenarios shown in Table 12.

Table 12: Power for Detecting Observed Seroprotection Proportions Given a True Seroprotection Proportion of 70% or 60%

True Seroprotection Proportion (%)	Observed Seroprotection Proportion (%)	Group Sample Size		
		N=60	N=120	N=180
70	80	32.3	64.1	84.7
	85	71.6	96.8	99.8
	90	96.6	>99.9	>99.9
60	80	92.3	99.8	>99.9
	85	99.4	>99.9	>99.9
	90	>99.9	>99.9	>99.9

13.3. Statistical Considerations

13.3.1. Covariates

Since no statistical models will be used for evaluation of the primary and secondary endpoints, adjustments for covariates will not be necessary.

13.3.2. Multicenter Studies

No by-site analyses are planned for this study.

13.3.3. Multiple Comparisons and Multiplicity

All safety and immunogenicity comparisons of treatment groups are considered exploratory in nature. As such, no adjustments will be required for multiple comparisons.

13.3.4. Subgroup Analyses

Safety and immunogenicity analyses will be evaluated by age group, participants 18 through 64 years old, and greater than or equal to 65 years old. All exploratory analyses, including any subgroups that require additional consideration, will be discussed in the SAP.

13.3.5. Missing Data

Standard procedures will be used to ensure that the data are as complete and accurate as possible. Due to the exploratory nature of this study, all descriptive summaries will be based upon all available data, and no imputation will be done.

13.4. Procedures for Documenting Deviations from Planned Analyses

The principal features of the design of this study and of the plan for statistical analysis of the data are outlined in this protocol. Additional details will be included in the SAP before initiating analyses. Any changes to that plan will be documented in the final clinical study report and will be approved by BARDA before being initiated.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Inspection of Records

BARDA, its designees, other authorized representatives of BARDA, Rho or its designees, ICON or its designees, representatives of the IRB, and/or regulatory agencies may inspect all source documents and records required to be maintained by the site investigator, including but not limited to, medical (office, clinic, or hospital) and pharmacy records for the participants in this study, all source documents, eCRFs, IRB submissions and approvals, study vaccine accountability logs, study vaccine temperature monitoring logs, regulatory documents, correspondence, and all other essential documents. The clinical trial site will permit site visits and access to (and when required by applicable law to copy) such records.

The site investigator also agrees to promptly notify BARDA and other authorized representatives of the sponsor of any inspections scheduled by any regulatory authority, or audits by other parties and promptly forward copies of any reports received to BARDA.

14.2. Institutional Review Board

A copy of the protocol, informed consent forms (ICFs), participant diary, any other participant facing documents, and any proposed advertising/recruitment materials will be submitted to the central IRB for written approval. Initial IRB approval and all materials approved by the IRB for this study, including the participant consent form and recruitment materials, must be maintained by the site investigator and made available for inspection.

15. QUALITY CONTROL AND QUALITY ASSURANCE

Quality assurance includes all the planned and systematic actions that are established to ensure that the clinical trial is performed and the data are generated, documented (recorded), and reported according to ICH GCP and local/regional regulatory standards.

To ensure the reliability of study data, the participating site(s) will have a plan in place to describe:

- routine internal QC and QA activities for the purposes of measuring, documenting and reporting study conduct, protocol adherence, human subjects' protections, and reliability of the protocol-driven data collected;
- a process for addressing in a timely manner any data quality issues (i.e., collecting, recording and reporting data), systemic issues (i.e., protocol conduct, non-compliance, human subject protections), and implementation of corrective and preventative action (CAPA) procedures.

A quality assurance representative from BARDA (or designee), who is independent of and separated from routine monitoring, may periodically arrange audits of the clinical trial by reviewing the data obtained and procedural aspects. These audits may include on site or remote audits and source data checks. Direct access to source documents is required for the purpose of these periodic audits.

15.1. Data Quality Assurance

Before enrolling any participants in this study, the site investigator will review the protocol, investigator's brochures for Egg-A/Astrakhan/3212/2020 (H5N8), Egg-A/bar-headed goose/Qinghai Lake/1A/2005 (H5N1), AS03A, and MF59, the eCRFs and instructions for their completion, the procedure for obtaining informed consent, and the procedure for reporting AEs, SAEs, MAAEs, and pIMDs.

As part of their responsibilities assumed by participating in the study, the site investigator agrees to maintain adequate source documents for the participants treated as part of their research under this protocol. In addition, the site investigator agrees to provide access to those records to BARDA's study monitor and auditor. Study monitors will verify information in the eCRFs against the source documents.

Data collected at the study site will be entered accurately and contemporaneously by study staff into a 21 CFR 11-compliant, internet-based, remote data entry system, which is backed up nightly. Data will be provided using the participant's unique identification number, not name or initials; Rho will not collect personally identifying information such as the participant's name or social security number. Participants will provide demographic information such as race, ethnicity, sex at birth, and age. All elements of data entry (e.g., time, date, verbatim text, and the person performing the data entry) will be recorded within the remote data entry system's audit trail to allow all data changes in the database to be monitored and maintained in accordance with federal regulations. Data collected by the laboratories will be transferred electronically directly from the laboratory to Rho using standard secure data transfer procedures. The analysis datasets will incorporate data from both sources. Data collected by Rho will be held in the strictest

confidence and are protected from access that could reveal personal information about any participant in the study.

Clinical data management and data cleaning procedures (e.g., resolving errors and inconsistencies in the data) will be performed in accordance with applicable Rho and/or BARDA standards and validation plans to ensure the integrity of the data. Adverse events (including SAEs, MAAEs, and pIMDs) and concomitant medication terms will be coded using the MedDRA and the World Health Organization Drug dictionaries, respectively.

After study monitors verify the data and prior to the end of study analysis, the site investigator must sign each eCRF at the participant level to confirm the integrity of the data recorded.

After database lock, each study site will receive an electronic copy of all their site-specific eCRF data as entered into the remote data entry system for the study, including full discrepancy and audit history. Additionally, all of the study's analysis datasets will be sent to BARDA electronically for storage. Rho will maintain a duplicate copy for its records and will upload a copy to the BARDA Clinical Studies Network (CSN) archive.

15.2. Study Monitoring

Site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently IRB/IEC approved protocol/amendment(s), ICH GCP, and applicable regulatory requirement(s). Clinical monitoring also verifies any critical study procedures are completed following specific instructions in ancillary documents referenced in the protocol.

Monitoring for this study will be performed by ICON, BARDA's authorized representative. Details of clinical site monitoring are documented in a monitoring plan. The monitoring plan describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports. Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, eCRFs, ICFs, medical and laboratory reports, site study vaccine storage records, training records, and protocol and GCP compliance. Site monitors will have access to each participating site, study personnel, and all study documentation according to the monitoring plan. Study monitors will meet with site investigators to discuss any problems and outstanding issues and will document site visit findings and discussions.

15.3. Protocol Deviations

15.3.1. Protocol Deviation Definition

A protocol deviation is any noncompliance with the IRB-approved study protocol, ICH GCP guidelines, or protocol-specific MOPs. Any deviation that affects the rights or safety of the participant or the integrity of the data will be considered a major protocol deviation. Prospective permission to deviate from protocol requirements, also known as protocol waivers or exemptions, will not be granted for this study.

15.3.2. Reporting and Managing Deviations

The site investigator has the responsibility to identify, document, and report deviations. Protocol deviations may also be identified during site monitoring visits or during other forms of study conduct review. All deviations, regardless of the cause, must be documented in accordance with GCP. Documentation at a minimum, will include the date the deviation occurred, the date it was identified, a description of the deviation, whether the deviation resulted in an AE/SAE/MAAE/pIMD, and documentation of a corrective action plan. In addition, the site investigator will report noncompliance to the IRB/IEC, as applicable.

Rho, ICON, and/or BARDA may request discussion with the site investigator to determine the effect of any major protocol deviation on a study participant and his/her further study participation, the effect of the deviation on the overall study, and corrective actions.

16. REGULATORY AND ETHICAL CONSIDERATIONS

16.1. Ethics Review

Before study initiation, each site will obtain central IRB approval for this protocol; ICF(s); participant recruitment materials; the participant diary and any other written information to be provided to participants; information about payments and compensation available to participants; and any other documents that the IRB may require to fulfill its responsibilities. Any amendments to those documents will require IRB approval before implementation except for changes necessary to eliminate an immediate hazard to a participant.

Each individual site will be reviewed and approved by the IRB prior to the shipment of study vaccine to, and the activation of, each individual site. Only institutions holding a current US Federal-wide Assurance issued by the Office for Human Research Protections at HHS may participate in the study.

IRB review and approval of protocol documents will occur at least annually throughout the enrollment and follow-up of participants, as per applicable regulations and the IRB.

The site investigator will promptly report all unanticipated problems involving risks to participants to the IRB.

The site investigator will notify the IRB of events such as deviations, SAEs, etc. as applicable to the IRB policy.

Participants may be compensated for their participation in this study. Compensation will be in accordance with the IRB's policies and procedures, and subject to IRB approval.

16.2. Ethical Conduct of the Study

The site investigator should conduct the study in accordance with this protocol, the Declaration of Helsinki, current ICH GCP guidelines, US 21 CFR Part 50 (Protection of Human Subjects) and Part 56 (Institutional Review Boards).

16.3. Written Informed Consent

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continuing throughout the individual's trial participation. Before any study procedures are performed, informed consent will be obtained and documented. Potential participants will receive a concise and focused presentation of key information about the clinical trial, verbally and with a written consent form. The key information about the purpose of the study, the procedures and experimental aspects of the study, study interventions/products, probability for random assignment to treatment groups, risks and discomforts, the expected duration of the participant's participation in the trial, any expected benefits to the participant, and alternative treatments and procedures that may be available to the participant. The explanation will be organized and presented in lay terminology and language that facilitates understanding why one might or might not want to participate.

Participants 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. Participants will be informed of the anticipated financial expenses,

if any, to the participant for participating in the trial, as well as any anticipated prorated payments, if any, to the participant for participating in the trial. They will be informed of whom to contact (e.g., the site investigator) for answers to any questions relating to the research project. Information will also include the foreseeable circumstances and/or reasons under which the participant's participation in the trial may be terminated. The participants 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 participant is otherwise entitled.

Participants will be informed that records identifying the participant 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 participant's identity will remain confidential. Participants will be informed whether private information collected from this research and/or specimens will be used for additional research, even if identifiers are removed.

Participants will be informed that the monitor(s), auditor(s), IRB, BARDA, and regulatory authority(ies) will be granted direct access to the participant's original medical records for verification of clinical trial procedures and/or data without violating the confidentiality of the participant, to the extent permitted by the applicable laws and regulations, and that, by signing a written ICF, the participant is authorizing such access.

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

Participants will be informed of the Public Readiness and Emergency Preparedness Act (PREP Act) and the Countermeasures Injury Compensation Program (CICP) (Appendix 4).

Informed consent forms will be IRB-approved, and participants will be asked to read and review the consent form. Participants must sign the ICF prior to starting any study procedures being done specifically for this trial. Once signed, a copy of the ICF will be given to the participant(s) for their records.

New information will be communicated by the site investigator to participants who consent to participate in this trial in accordance with IRB requirements. The informed consent document will be updated, and participants will be re-consented per IRB requirements, if necessary. Using the ICF, participants who consent to participate in this study will be asked to consent to the following:

- Permission to be contacted with a request to participate in future clinical studies of participants who have been vaccinated against influenza H5N8 or H5N1.
- Permission to store serum for future investigations. Serum samples collected for future investigations will be stored indefinitely. Participants who provide consent may withdraw that consent for future investigations by contacting the study doctor identified on the consent form. After their participation in the study has ended, participants can contact BARDA [redacted]. Serum will be destroyed, but any data that have already been collected from analysis of serum samples will remain a part of the research database.

17. DATA HANDLING AND RECORD KEEPING

17.1. Confidentiality

Participant confidentiality is strictly held in trust by the participating site investigators, their staff, and the sponsor(s) and their designees. This confidentiality is extended to cover clinical information relating to participants, test results of biological samples, and all other information generated during participation in the study. No identifiable information concerning participants in the study will be released to any unauthorized third party. Participant confidentiality will be maintained when study results are published or discussed in conferences.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, and/or regulatory agencies may inspect all documents and records required to be maintained by the site investigator, including but not limited to, medical (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical trial site will permit access to such records.

All source records including electronic data will be stored in secured systems in accordance with institutional policies and federal regulations.

All study data and research specimens that leave the site (including any electronic transmission of data) will be identified only by a coded number that cannot be linked to a participant.

17.2. Retention of Records

The site investigator should retain all documentation relating to the study (including but not limited to ICFs, source documentation, study vaccine records, eCRFs, and essential documents) for a period of 2 years after the last marketing application approval for the study product for the indication for which it is being investigated, or if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

If this requirement differs from any local regulations, the local regulations will take precedence unless the local retention policy is less than 2 years.

At study closure, the site investigator must inform BARDA, or designee, of the long-term storage location of the study's records. Following study closure, the site investigator must inform BARDA if that location changes (e.g., the site investigator leaves the institution where the study was conducted).

No study records will be destroyed without prior authorization from BARDA.

18. PUBLICATION POLICY

BARDA will be responsible for publication activities and for defining the manuscript/presentation development process, the number and order of authors, the publication/scientific meeting to which it will be submitted, and other related issues. BARDA has final approval authority over all such issues.

Data are the property of BARDA and cannot be published without prior authorization from BARDA, but data and publication thereof will not be unduly withheld.

All applicable clinical trials supported by BARDA must be registered on ClinicalTrials.gov, no later than 21 days after the enrollment of the first participant. This will include a description of the clinical trial as required by US Law. This web site will not include information that can identify participants. Results information from those trials must be submitted no later than one year after the trial's primary completion date.

As required, the following will be posted on ClinicalTrials.gov: Protocol, ICF (that has been used to enroll participants), and SAP.

19. LIST OF REFERENCES

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20. PROTOCOL AMENDMENT HISTORY

Table 13: Protocol Amendment History

Version	Date	Description of Change	Brief Rationale
1.0	25 April 2024	N/A	Initial version
2.0	20 May 2024	Revisions to descriptions of study vaccine mixing and study product information.	Incorporated correct study product information and revised mixing protocol.
3.0	05 August 2024	Revisions to inclusion criterion 5 and to Section 12.1.5.1	Revised language for duration of contraception to require adequate methods to be used for 4 weeks after second vaccination. Added language for chemistry labs to include fasting prior to sample collection and instructions for how to manage values outside the ULN.

21. APPENDICES

APPENDIX 1. SCHEDULE OF ASSESMENTS

APPENDIX 2. TABLES FOR CLINICAL AND LABORATORY ABNORMALITIES

APPENDIX 3. LIST OF POTENTIALLY IMMUNE-MEDIATED DISEASES

APPENDIX 4. PUBLIC READINESS AND EMERGENCY PREPAREDNESS ACT

APPENDIX 1. SCHEDULE OF ASSESSMENTS

Study Visit and Day	Screening	V1/D1	V2/D8	V3/D22	V4/D29	V5/D43	V6/D203 (EoS Visit)	ET[a]	Unscheduled[b]
Visit Window based on vaccination day	**-14 to D-3**		**V1+7d, ±1**	**V1+21d, -3/+7**	**V3+7d, ±1**	**V3+21d, ±3**	**V3+181d, ±7**	**N/A**	**N/A**
Obtain informed consent[c]	X								
Demographics	X								
Inclusion and exclusion criteria[d]	X	X[e]		X[e]					
Medical history	X								
Prior and concomitant medications[f]	X	X[e]	X[g]	X[e,g]	X[g]	X[g]	X	X	X
Height and weight	X								
Vital signs[h]	X	X		X		X		X	X[i]
Physical examination	X								
Targeted physical examination		X[e]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]
Pregnancy test[k]	X	X[e]		X[e]					
Safety labs (12 mL blood)[l]	X		X		X			X[i]	X[i]
Immunogenicity profile (approximately 5 mL blood)	X			X[e]		X	X		
Serum samples for future research (approximately 35 mL blood)	X			X[e]		X	X		
Randomization		X							
Vaccination		X		X					
Monitor participant for 30 minutes following vaccination[m]		X		X					
Examine vaccination site		X[n]	X	X[n]	X			X[o]	X[o]
AE assessment		X[p]	X	X[p]	X	X	X	X[q]	X
Dispense diary and accompanying materials[r]		X	X	X	X				X[s]
Review/collect diary			X	X	X	X		X[s]	X[s]

AE = adverse event; D = day; eCRF = electronic case report form; EoS = end of study; ET = early termination; MAAE = medically attended adverse event; N/A = not applicable; pIMD = potentially immune-mediated disease; TEAE = treatment-emergent adverse event; SAE = serious adverse event; V = visit

[a] Early Termination Visit procedures will be performed for participants who discontinue prior to the end of study.

[b] Unscheduled Visit procedures will be performed when a participant must be seen for a visit that is not otherwise stipulated in the schedule.

[c] Prior to the completion of any study-related procedures.

[d] All Inclusion/Exclusion Criteria will be assessed at the Screening Visit. A subset of the criteria will be reassessed at each visit at which a vaccine dose is to be administered to confirm continued participant eligibility.

[e] Prior to vaccination.

[f] All medications and therapies the participant is receiving at the time of the Screening Visit and any vaccines received within 90 days prior to the Screening Visit will be recorded in the participant's eCRF. Concomitant medications will include ongoing medications at Visit 1 and at any subsequent visits. Changes in medications and any vaccinations received since the last visit will be recorded at subsequent visits.

[g] Obtained by interview and by review of the diary card completed by the participant.

[h] Vital sign measurements include oral temperature, pulse rate, respiratory rate, and diastolic and systolic blood pressure. Vital signs will be measured before blood is collected. Blood pressure will be measured after participant is seated for at least 5 minutes. Vital signs will be taken both pre-vaccination and 30 ±5 minutes post-vaccination on a vaccination day. Prior to the second vaccination (Visit 3), if a participant's oral temperature is above 100.4ºF, indicating acute illness, the participant may be reassessed for eligibility a minimum of 24 hours later.

[i] If clinically indicated. The site investigator in consultation with the medical monitor will determine whether safety laboratory assessments should be completed.

[j] Targeted physical examination will be performed if clinically indicated based on review of interim health status and/or clinical laboratory assessments.

[k] An onsite urine pregnancy test will be performed for all women of childbearing potential at the Screening Visit and within 24 hours prior to each vaccination. Pregnancy test results must be final and negative prior to vaccination. Additionally, a urine pregnancy test should be performed at any time during study participation if pregnancy is suspected.

[l] Clinical safety laboratory tests include a complete blood count with differential, coagulation (partial thromboplastin time and prothrombin time (international normalized ratio) and chemistry including alanine aminotransferase, albumin, alkaline phosphatase, aspartate aminotransferase, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, glucose (random, serum), potassium, sodium, total bilirubin, and total protein.

[m] At Visits 1 and 3, participants will be monitored for solicited and unsolicited TEAEs, SAEs, and MAAEs for at least 30 minutes after vaccination. Any concomitant medications taken for these events will be recorded.

[n] At Visits 1 and 3, a 30 ±5-minute post-vaccination injection site examination will be completed for erythema/redness and induration/swelling and to monitor for pain.

[o] If the ET or Unscheduled Visit occurs within 7 days after either of the 2 study vaccinations.

[p] At Visit 1, AEs will be collected during the immediate 30-minute observation period following study vaccination. At Visit 3, AEs will be collected both prior to vaccination and during the immediate 30-minute observation period following study vaccination.

[q] If participant declines to participate in an onsite ET visit, study staff should attempt to collect AE/SAE/MAAE/pIMD and pregnancy information by phone.

[r] Participants will complete diary entries beginning on the day of vaccination through Day 43. Participants will be instructed to fill in the diary at the same time each day to capture observations, which will include solicited local and systemic reactions through 8 days after each vaccination, inclusive of the vaccination day, and all unsolicited symptoms/complaints through Day 43. Any abnormal findings not resolved at the time of diary collection will be followed per Section 12.3.2 during follow-up AE assessments. Thermometers and measuring tools (rulers) will be provided to participants at Visit 1 and replenished as needed. Only SAEs, MAAEs, and pIMDs will be collected after Day 43 until the EoS Visit (Day 203).

[s] If a participant has a diary in their possession at an Unscheduled Visit, the diary will be reviewed and collected, and a new one will be issued if the schedule requires that they still fill out a diary or if a finding is unresolved, as described above.

APPENDIX 2. TABLES FOR CLINICAL AND LABORATORY ABNORMALITIES

The tables for clinical and laboratory abnormalities are presented in Appendix Table 2A and Appendix Table 2B, respectively, according to the FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007). All parameters may not be collected in each vaccine trial. Please refer to the Schedule of Events in Appendix 1 for a list of parameters collected in this trial.

Appendix Table 2A: Tables for Clinical Abnormalities

Local Reactivity Clinical Abnormalities

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Emergency room visit or hospitalization
Erythema/redness[a]	2.5-5 cm	5.1-10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/swelling[b]	2.5-5 cm and does not interfere with activity	5.1-10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis

[a] In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
[b] Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Vital Sign Clinical Abnormalities

Vital Signs[a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C)[b] (°F)[b]	38.0-38.4 100.4-101.1	38.5-38.9 101.2-102.0	39.0-40 102.1-104	>40 >104
Tachycardia – beats per minute	101-115	116-130	>130	ER visit or hospitalization for arrhythmia
Bradycardia – beats per minute[c]	50-54	45-49	<45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) – mm Hg	141-150	151-155	>155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) – mm Hg	91-95	96-100	>100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85-89	80-84	<80	ER visit or hospitalization for hypotensive shock
Respiratory rate – breaths per minute	17-20	21-25	>25	Intubation

ER = emergency room

[a] Participant should be at rest for all vital sign measurements.

[b] Oral temperature; no recent hot or cold beverages or smoking.

[c] When resting heart rate is between 60 to 100 beats per minute. Use clinical judgment when characterizing bradycardia among some healthy participant populations, for example, conditioned athletes.

Systemic (General) Clinical Abnormalities

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1-2 episodes/24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2-3 loose stools or <400 g/24 hours	4-5 stools or 400-800 g/24 hours	6 or more watery stools or >800 g/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

ER = emergency room; IV = intravenous

Appendix Table 2B: Tables for Laboratory Abnormalities

Serum Laboratory Abnormalities

Serum[a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)[b]
Sodium – hyponatremia mEq/L	132-134	130-131	125-129	<125
Sodium – hypernatremia mEq/L	144-145	146-147	148-150	>150
Potassium – hyperkalemia mEq/L	5.1-5.2	5.3-5.4	5.5-5.6	>5.6
Potassium – hypokalemia mEq/L	3.5-3.6	3.3-3.4	3.1-3.2	<3.1
Glucose – hypoglycemia mg/dL	65-69	55-64	45-54	<45
Glucose – hyperglycemia Fasting - mg/dL Random - mg/dL	 100-110 110-125	 111-125 126-200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood urea nitrogen mg/dL	23-26	27-31	>31	Requires dialysis
Creatinine mg/dL	1.5-1.7	1.8-2.0	2.1-2.5	>2.5 or requires dialysis
Calcium-hypocalcemia mg/dL	8.0-8.4	7.5-7.9	7.0-7.4	<7.0
Calcium-hypercalcemia mg/dL	10.5-11.0	11.1-11.5	11.6-12.0	>12.0

Magnesium-hypomagnesemia mg/dL	1.3-1.5	1.1-1.2	0.9-1.0	<0.9
Phosphorus – hypophosphatemia mg/dL	2.3-2.5	2.0-2.2	1.6-1.9	<1.6
CPK - mg/dL	1.25-1.5 × ULN	1.6-3.0 × ULN	3.1-10 × ULN	>10 × ULN
Albumin – hypoalbuminemia g/dL	2.8-3.1	2.5-2.7	<2.5	–
Total protein – hypoproteinemia g/dL	5.5-6.0	5.0-5.4	<5.0	–
Alkaline phosphate – increase by factor	1.1-2.0 × ULN	2.1-3.0 × ULN	3.1-10 × ULN	>10 × ULN
Liver function tests – ALT, AST increase by factor	1.1-2.5 × ULN	2.6-5.0 × ULN	5.1-10 × ULN	>10 × ULN
Bilirubin – when accompanied by any increase in liver function test increase by factor	1.1-1.25 × ULN	1.26-1.5 × ULN	1.51-1.75 × ULN	>1.75 × ULN
Bilirubin – when liver function test is normal; increase by factor	1.1-1.5 × ULN	1.6-2.0 × ULN	2.0-3.0 × ULN	>3.0 × ULN
Cholesterol mg/dL	201-210	211-225	>226	-
Pancreatic enzymes – amylase, lipase	1.1-1.5 × ULN	1.6-2.0 × ULN	2.1-5.0 × ULN	>5.0 × ULN

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; ULN = upper limit of normal.

[a] The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

[b] The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example, a low sodium value that falls

within a Grade 3 parameter (125-129 mEq/L) should be recorded as a Grade 4 hyponatremia event if the participant had a new seizure associated with the low sodium value.

Hematological Laboratory Abnormalities

Hematology[a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (female) – g/dL	11.0-12.0	9.5-10.9	8.0-9.4	<8.0
Hemoglobin (female) change from baseline value – g/dL	Any decrease – 1.5	1.6-2.0	2.1-5.0	>5.0
Hemoglobin (male) – g/dL	12.5-13.5	10.5-12.4	8.5-10.4	<8.5
Hemoglobin (male) change from baseline value – g/dL	Any decrease – 1.5	1.6-2.0	2.1-5.0	>5.0
WBC increase – cell/mm^3	10,800-15,000	15,001-20,000	20,001-25,000	>25,000
WBC decrease – cell/mm^3	2,500-3,500	1,500-2,499	1,000-1,499	<1,000
Lymphocytes decrease – cell/mm^3	750-1 000	500-749	250-499	<250
Neutrophils decrease – cell/mm^3	1,500-2,000	1,000-1,499	500-999	<500
Eosinophils – cell/mm^3	650-1 500	1501-5 000	>5 000	Hypereosinophilic
Platelets decrease – cell/mm^3	125,000-140,000	100,000-124,000	25,000-99,000	<25,000

PT – increase by factor	1.0-1.10 × ULN	1.11-1.20 × ULN	1.21-1.25 × ULN	>1.25 x ULN
PTT – increase by factor	1.0-1.2 × ULN	1.21-1.4 × ULN	1.41-1.5 × ULN	>1.5 x ULN
Fibrinogen increase – mg/dL	400-500	501-600	>600	–
Fibrinogen decrease – mg/dL	150-200	125-149	100-124	<100 or associated with gross bleeding or disseminated intravascular coagulation

PPT = partial thromboplastin time; PT = prothrombin time; ULN = upper limit of normal; WBC = white blood cell
[a] The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Urine Laboratory Abnormalities

Urine[a]	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization or hyperglycemia
Blood (microscopic) – red blood cells per high power field	1-10	11-50	>50 and/or gross blood	Hospitalization or packed red blood cells transfusion

[a] The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

APPENDIX 3. LIST OF POTENTIALLY IMMUNE-MEDIATED DISEASES

MedDRA Term	Term Level
Acute cutaneous lupus erythematosus	PT
Acute disseminated encephalomyelitis	PT
Acute febrile neutrophilic dermatosis	PT
Acute flaccid myelitis	PT
Acute haemorrhagic leukoencephalitis	PT
Acute haemorrhagic oedema of infancy	PT
Acute macular neuroretinopathy	PT
Acute motor axonal neuropathy	PT
Acute motor-sensory axonal neuropathy	PT
Acute necrotising myelitis	PT
Addison's disease	PT
Administration site vasculitis	PT
AGEP-DRESS overlap	PT
Alopecia areata	PT
Alveolar proteinosis	PT
Ankylosing spondylitis	PT
Antibody-dependent enhancement	PT
Anti-glomerular basement membrane disease	PT
Anti-LRP2 nephropathy	PT
Anti-myelin-associated glycoprotein associated polyneuropathy	PT
Anti-neutrophil cytoplasmic antibody positive vasculitis	PT
Antiphospholipid syndrome	PT
Anti-RNA polymerase III antibody increased	PT
Anti-RNA polymerase III antibody positive	PT
Antisynthetase syndrome	PT
Aortitis	PT
Application site vasculitis	PT
Arteritis	PT
Arteritis coronary	PT

Arthritis enteropathic	PT
Arthritis reactive	PT
ASIA syndrome	PT
Atrophic thyroiditis	PT
Autoimmune anaemia	PT
Autoimmune aplastic anaemia	PT
Autoimmune arthritis	PT
Autoimmune blistering disease	PT
Autoimmune cerebellar ataxia	PT
Autoimmune cholangitis	PT
Autoimmune colitis	PT
Autoimmune demyelinating disease	PT
Autoimmune dermatitis	PT
Autoimmune disorder	PT
Autoimmune encephalopathy	PT
Autoimmune endocrine disorder	PT
Autoimmune enteropathy	PT
Autoimmune eye disorder	PT
Autoimmune haemolytic anaemia	PT
Autoimmune heparin-induced thrombocytopenia	PT
Autoimmune hepatitis	PT
Autoimmune hyperlipidaemia	PT
Autoimmune hypothyroidism	PT
Autoimmune inner ear disease	PT
Autoimmune lung disease	PT
Autoimmune lymphoproliferative syndrome	PT
Autoimmune myocarditis	PT
Autoimmune myositis	PT
Autoimmune nephritis	PT
Autoimmune neuropathy	PT
Autoimmune neutropenia	PT
Autoimmune pancreatitis	PT
Autoimmune pancytopenia	PT

Autoimmune pericarditis	PT
Autoimmune retinopathy	PT
Autoimmune thyroid disorder	PT
Autoimmune thyroiditis	PT
Autoimmune uveitis	PT
Autoinflammatory disease	PT
Axial spondyloarthritis	PT
Axonal and demyelinating polyneuropathy	PT
Axonal neuropathy	PT
Basedow's disease	LLT
Behcet's syndrome	PT
Bell's palsy	PT
Bickerstaffs encephalitis	PT
Birdshot chorioretinopathy	PT
Brachial plexopathy	PT
Bulbar palsy	PT
C1q nephropathy	PT
CANOMAD syndrome	PT
Capillaritis	PT
Capillary leak syndrome	PT
Caplan's syndrome	PT
Cardiac sarcoidosis	PT
Central nervous system lupus	PT
Central nervous system vasculitis	PT
Cerebral arteritis	PT
Cholangitis sclerosing	PT
Chronic autoimmune glomerulonephritis	PT
Chronic cutaneous lupus erythematosus	PT
Chronic inflammatory demyelinating polyradiculoneuropathy	PT
Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids	PT
Chronic pigmented purpura	PT
Clinically isolated syndrome	PT

Coeliac disease	PT
Cogan's syndrome	PT
Cold type haemolytic anaemia	PT
Colitis erosive	PT
Colitis microscopic	PT
Colitis ulcerative	PT
Collagen-vascular disease	PT
Concentric sclerosis	PT
Coombs positive haemolytic anaemia	PT
Cranial nerve disorder	PT
Cranial nerve palsies multiple	PT
Cranial nerve paralysis	PT
CREST syndrome	PT
Crohn's disease	PT
Cutaneous lupus erythematosus	PT
Cutaneous sarcoidosis	PT
Cutaneous vasculitis	PT
Demyelinating polyneuropathy	PT
Demyelination	PT
Dermatitis bullous	PT
Dermatitis herpetiformis	PT
Dermatomyositis	PT
Diffuse vasculitis	PT
Encephalitis allergic	PT
Encephalitis autoimmune	PT
Encephalitis brain stem	PT
Encephalitis haemorrhagic	PT
Encephalitis periaxialis diffusa	PT
Encephalitis post immunisation	PT
Encephalitis toxic	PT
Encephalomyelitis	PT
Endocrine ophthalmopathy	PT
Enhanced respiratory disease	PT

Enteropathic spondylitis	PT
Eosinophilic fasciitis	PT
Eosinophilic granulomatosis with polyangiitis	PT
Erythema induratum	PT
Erythema multiforme	PT
Erythema nodosum	PT
Evans syndrome	PT
Expanded disability status scale score decreased	PT
Expanded disability status scale score increased	PT
Facial paralysis	PT
Facial paresis	PT
Felty's syndrome	PT
Fibrillary glomerulonephritis	PT
Fulminant type 1 diabetes mellitus	PT
Giant cell arteritis	PT
Giant cell myocarditis	PT
Glomerulonephritis membranoproliferative	PT
Glomerulonephritis membranous	PT
Glomerulonephritis rapidly progressive	PT
Glossopharyngeal nerve paralysis	PT
Goodpasture's syndrome	PT
Gout	PT
Gouty arthritis	PT
Gouty tophus	PT
Granulomatosis with polyangiitis	PT
Granulomatous dermatitis	PT
Graves' disease	PT
Guillain-Barre syndrome	PT
Haemorrhagic occlusive retinal vasculitis	PT
Haemorrhagic vasculitis	PT
Hashimoto's encephalopathy	PT
Hashitoxicosis	PT
Henoch-Schonlein purpura	PT

Henoch-Schonlein purpura nephritis	PT
Hypersensitivity vasculitis	PT
Hypoglossal nerve paralysis	PT
Hypoglossal nerve paresis	PT
Idiopathic inflammatory myopathy	PT
Idiopathic interstitial pneumonia	PT
Idiopathic pulmonary fibrosis	PT
IgA nephropathy	PT
IgM nephropathy	PT
IIIrd nerve paralysis	PT
IIIrd nerve paresis	PT
Immune-mediated adrenal insufficiency	PT
Immune-mediated adverse reaction	PT
Immune-mediated arthritis	PT
Immune-mediated cholangitis	PT
Immune-mediated cholestasis	PT
Immune-mediated cystitis	PT
Immune-mediated cytopenia	PT
Immune-mediated dermatitis	PT
Immune-mediated encephalitis	PT
Immune-mediated encephalopathy	PT
Immune-mediated endocrinopathy	PT
Immune-mediated enterocolitis	PT
Immune-mediated gastritis	PT
Immune-mediated hepatic disorder	PT
Immune-mediated hepatitis	PT
Immune-mediated hyperthyroidism	PT
Immune-mediated hypophysitis	PT
Immune-mediated hypothyroidism	PT
Immune-mediated lung disease	PT
Immune-mediated myasthenia gravis	PT
Immune-mediated myelitis	PT
Immune-mediated myocarditis	PT

Immune-mediated myositis	PT
Immune-mediated nephritis	PT
Immune-mediated neurological disorder	PT
Immune-mediated neuropathy	PT
Immune-mediated oesophagitis	PT
Immune-mediated optic neuritis	PT
Immune-mediated pancreatitis	PT
Immune-mediated pericarditis	PT
Immune-mediated polyserositis	PT
Immune-mediated renal disorder	PT
Immune-mediated scleritis	PT
Immune-mediated thyroiditis	PT
Immune-mediated uveitis	PT
Immune thrombocytopenia	PT
Immunoglobulin 04 related disease	PT
Inclusion body myositis	PT
Inflammatory bowel disease	PT
Injection site vasculitis	PT
Insulin autoimmune syndrome	PT
Interstitial granulomatous dermatitis	PT
Interstitial lung disease	PT
Intramyelinic oedema	PT
IVth nerve paralysis	PT
IVth nerve paresis	PT
Juvenile idiopathic arthritis	PT
Juvenile polymyositis	PT
Juvenile psoriatic arthritis	PT
Juvenile spondyloarthritis	PT
Kawasaki's disease	PT
Keratoderma blenorrhagica	PT
Langerhans' cell histiocytosis	PT
Laryngeal rheumatoid arthritis	PT
Latent autoimmune diabetes in adults	PT

Leukoencephalomyelitis	PT
Leukoencephalopathy	PT
Lewis-Sumner syndrome	PT
Lichen planopilaris	PT
Lichen planus	PT
Lichen planus pemphigoides	PT
Limbic encephalitis	PT
Linear IgA disease	PT
Liver sarcoidosis	PT
Loefgren syndrome	PT
Lumbosacral radiculoplexus neuropathy	PT
Lupoid hepatic cirrhosis	PT
Lupus anticoagulant hypoprothrombinaemia syndrome	PT
Lupus cystitis	PT
Lupus encephalitis	PT
Lupus endocarditis	PT
Lupus enteritis	PT
Lupus hepatitis	PT
Lupus-like syndrome	PT
Lupus myocarditis	PT
Lupus myositis	PT
Lupus nephritis	PT
Lupus pancreatitis	PT
Lupus pleurisy	PT
Lupus pneumonitis	PT
Lupus vasculitis	PT
Lymphocytic hypophysitis	PT
MAGIC syndrome	PT
Marburg's variant multiple sclerosis	PT
Marine Lenhart syndrome	PT
Melkersson-Rosenthal syndrome	PT
Membranous-like glomerulopathy with masked IgG-kappa deposits	PT
Mesangioproliferative glomerulonephritis	PT

Metastatic cutaneous Crohn's disease	PT
Microscopic enteritis	PT
Microscopic polyangiitis	PT
Miller Fisher syndrome	PT
Mixed connective tissue disease	PT
Mononeuritis	PT
Mononeuropathy multiplex	PT
Morphoea	PT
Morvan syndrome	PT
Mucous membrane pemphigoid	PT
Multifocal motor neuropathy	PT
Multiple sclerosis	PT
Multiple sclerosis pseudo relapse	PT
Multiple sclerosis relapse	PT
Multiple sclerosis relapse prophylaxis	PT
Multisystem inflammatory syndrome	PT
Multisystem inflammatory syndrome in adults	PT
Multisystem inflammatory syndrome in children	PT
Muscular sarcoidosis	PT
Myasthenia gravis	PT
Myasthenia gravis crisis	PT
Myasthenic syndrome	PT
Myelin oligodendrocyte glycoprotein antibody-associated disease	PT
Myelitis	PT
Myelitis transverse	PT
Myocarditis	PT
Myopericarditis	PT
Narcolepsy	PT
Neuralgic amyotrophy	PT
Neuritis	PT
Neuritis cranial	PT
Neuromyelitis optica pseudo relapse	PT
Neuromyelitis optica spectrum disorder	PT

Neuropsychiatric lupus	PT
Neurosarcoidosis	PT
Nodular vasculitis	PT
Noninfectious myelitis	PT
Noninfective encephalitis	PT
Noninfective encephalomyelitis	PT
Noninfective oophoritis	PT
Ocular myasthenia	PT
Ocular pemphigoid	PT
Ocular sarcoidosis	PT
Ocular vasculitis	PT
Oculofacial paralysis	PT
Olfactory nerve disorder	PT
Optic ischaemic neuropathy	PT
Optic neuritis	PT
Optic neuropathy	PT
Optic perineuritis	PT
Overlap syndrome	PT
Palindromic rheumatism	PT
Palisaded neutrophilic granulomatous dermatitis	PT
Palpable purpura	PT
Panencephalitis	PT
Paresis cranial nerve	PT
Pemphigoid	PT
Pemphigus	PT
Pericarditis	PT
Pericarditis lupus	PT
Pericarditis rheumatic	PT
Peripheral spondyloarthritis	PT
Peritonitis lupus	PT
Pernicious anaemia	PT
Pleuroparenchymal fibroelastosis	PT
Polyarteritis nodosa	PT

Polychondritis	PT
Polyglandular autoimmune syndrome type I	PT
Polyglandular autoimmune syndrome type II	PT
Polyglandular autoimmune syndrome type III	PT
Polymyalgia rheumatica	PT
Polymyositis	PT
Polyneuropathy idiopathic progressive	PT
Primary biliary cholangitis	PT
Primary progressive multiple sclerosis	PT
Proctitis ulcerative	PT
Progressive facial hemiatrophy	PT
Progressive multiple sclerosis	PT
Progressive relapsing multiple sclerosis	PT
Psoriasis	PT
Psoriatic arthropathy	PT
Pulmonary fibrosis	PT
Pulmonary renal syndrome	PT
Pulmonary sarcoidosis	PT
Pulmonary vasculitis	PT
Pyoderma gangrenosum	PT
Pyostomatitis vegetans	PT
Radiculitis brachial	PT
Radiologically isolated syndrome	PT
Rasmussen encephalitis	PT
Raynaud's phenomenon	PT
Relapsing multiple sclerosis	PT
Relapsing-remitting multiple sclerosis	PT
Renal arteritis	PT
Renal vasculitis	PT
Retinal occlusive vasculitis	PT
Retinal vasculitis	PT
Reynold's syndrome	PT
Rheumatic brain disease	PT

Rheumatic disorder	PT
Rheumatoid arthritis	PT
Rheumatoid arthritis-associated interstitial lung disease	PT
Rheumatoid bursitis	PT
Rheumatoid lung	PT
Rheumatoid meningitis	PT
Rheumatoid neutrophilic dermatosis	PT
Rheumatoid nodule	PT
Rheumatoid pleuritis	PT
Rheumatoid scleritis	PT
Rheumatoid vasculitis	PT
Sarcoidosis	PT
Sarcoidosis of lymph node	PT
Satoyoshi syndrome	PT
Sclerodactylia	PT
Scleroderma	PT
Scleroderma associated digital ulcer	PT
Scleroderma renal crisis	PT
Secondary progressive multiple sclerosis	PT
Segmented hyalinising vasculitis	PT
Shrinking lung syndrome	PT
Silent thyroiditis	PT
Sjogren's syndrome	PT
SJS-TEN overlap	PT
SLE arthritis	PT
Spondylitis	PT
Spondyloarthropathy	PT
Stevens-Johnson syndrome	PT
Still's disease	PT
Stoma site vasculitis	PT
Subacute cutaneous lupus erythematosus	PT
Subacute inflammatory demyelinating polyneuropathy	PT
Susac's syndrome	PT

Sympathetic ophthalmia	PT
Systemic lupus erythematosus	PT
Systemic lupus erythematosus disease activity index abnormal	PT
Systemic lupus erythematosus disease activity index decreased	PT
Systemic lupus erythematosus disease activity index increased	PT
Systemic lupus erythematosus rash	PT
Systemic scleroderma	PT
Systemic sclerosis pulmonary	PT
Takayasu's arteritis	PT
Terminal ileitis	PT
Testicular autoimmunity	PT
Thromboangiitis obliterans	PT
Thrombocytopenic purpura	PT
Thrombosis with thrombocytopenia syndrome	PT
Thrombotic thrombocytopenic purpura	PT
Tongue paralysis	PT
Toxic epidermal necrolysis	PT
Trigeminal nerve paresis	PT
Trigeminal palsy	PT
Tubulointerstitial nephritis and uveitis syndrome	PT
Tumefactive multiple sclerosis	PT
Type 1 diabetes mellitus	PT
Uhthoffs phenomenon	PT
Ulcerative keratitis	PT
Undifferentiated connective tissue disease	PT
Undifferentiated spondyloarthritis	PT
Urticarial vasculitis	PT
Uveitis	PT
Vaccination site vasculitis	PT
Vaccine associated enhanced disease	LLT
Vaccine associated enhanced respiratory disease	LLT
Vagus nerve paralysis	PT
Vascular purpura	PT

Vasculitic rash	PT
Vasculitic ulcer	PT
Vasculitis	PT
Vasculitis gastrointestinal	PT
Vasculitis necrotising	PT
Vlth nerve paralysis	PT
Vlth nerve paresis	PT
Vitiligo	PT
Vocal cord paralysis	PT
Vocal cord paresis	PT
Vogt-Koyanagi-Harada disease	PT
Warm autoimmune haemolytic anaemia	PT
Xlth nerve paralysis	PT

Abbreviations: LLT = lowest level term; PT = preferred term.

APPENDIX 4. PUBLIC READINESS AND EMERGENCY PREPAREDNESS ACT

The following language applies only to Clinical Research Sites located in the United States.

Public Readiness and Emergency Preparedness (PREP) Act

The study vaccine antigens Egg-A/Astrakhan/3212/2020 (H5N8) and Egg-A/bar-headed goose/Qinghai Lake/1A/2005 (H5N1), study vaccine adjuvants AS03A and MF59, and the efforts for this clinical trial are covered under the Public Readiness and Emergency Preparedness Act (PREP Act) and the Declaration issued by the Secretary of the US Department of Health and Human Services under that Act. Under the PREP Act and the Declaration, covered persons (such as manufacturers, distributers, program planners, and other qualified persons who prescribe, administer or dispense study product) are immune from liability from the administration, or use of a covered countermeasure, such as Egg-A/Astrakhan/3212/2020 (H5N8), Egg-A/bar-headed goose/Qinghai Lake/1A/2005 (H5N1), AS03A, and MF59. The PREP Act provides immunity for covered persons from liability, unless the injury was caused by willful misconduct.

The PREP Act also established the Countermeasures Injury Compensation Program (CICP) to provide compensation for serious injuries or death that occur as the direct result of the administration or use of certain countermeasures. Any requests for compensation must be filed within one year of the administration or use of the covered countermeasure. Requests for Benefits must be made to the Health Resources and Services Administration's (HRSA) Countermeasures Injury Compensation Program (http://www.hrsa.gov/cicp/) by filing a Request for Benefits Form and all required medical records and supporting documentation. Additional information on filing a Request for Benefits is available on the CICP's website at http://www.hrsa.gov/cicp/. Compensation may then be available for reasonable and necessary medical benefits, lost wages and/or death benefits to eligible individuals for certain injuries in accordance with regulations published by the Secretary of HHS (found at 42 CFR part 110).

If an individual suffers a serious physical injury or death from the administration or use of a covered countermeasure in this study, the individual, the individual's legal or personal representative, the administrator/executor of a deceased individual's estate, or certain survivors may request benefits from the CICP. A serious physical injury means an injury that warranted hospitalization (whether or not the person was actually hospitalized) or that led to a significant loss of function or disability. The CICP is the payer of last resort. This means that it only covers expenses or provides benefits that other third-party payers (such as health insurance, the Department of Veterans Affairs, or Workers' Compensation programs) do not have an obligation to pay.

If the Secretary of HHS does not make a final determination on the individual's request within 240 days, or if the individual decides not to accept the compensation, the injured individual or his representative may pursue a tort claim in the US District Court for the District of Columbia, but only if the claim involves willful misconduct and meets the other requirements for suit under the PREP Act. Any award is reduced by any public or private insurance or worker's compensation available to the injured individual. Awards for non-economic damages, such as pain, suffering, physical impairment, mental anguish, and loss of consortium are also limited. If the individual accepts compensation, or if there is no willful misconduct, then the individual does not have a tort claim that can be filed in a US Federal or a State court.