CLINICAL STUDY PROTOCOL

Randomized, Double-Blinded, Phase 2 Study to Assess Safety and Immunogenicity of Homologous and Heterologous Prime-Boost Vaccination Strategies With Stockpiled Inactivated Monovalent Influenza A(H5) Vaccines Administered Intramuscularly With Either AS03 or MF59® as Adjuvant

BP-I-16-005

Sponsor:	Biomedical Advanced Research and Development Authority (BARDA) 200 Independence Avenue, S.W. Room 640-G Washington, DC 20201
[redacted]	[redacted]
[redacted]	[redacted]
IND Number:	[redacted]
Version of Protocol:	2.0
Date of Protocol:	Amendment 1: 26 February 2018
Previous Versions and Dates:	Version 1.0, 19 October 2017 Version 1.1, 17 November 2017 Version 1.2, 26 January 2018

CONFIDENTIAL

The study will be conducted according to the International Council for Harmonisation harmonised tripartite guideline E6(R1): Good Clinical Practice.

Protocol Approval – Sponsor Signatory

Study Title Randomized, Double-Blinded, Phase 2 Study to Assess Safety and Immunogenicity of Homologous and Heterologous Prime-Boost Vaccination Strategies With Stockpiled Inactivated Monovalent Influenza A(H5) Vaccines Administered Intramuscularly With Either AS03 or MF59® as Adjuvant

Protocol Number BP-I-16-005

Protocol Date 26 February 2018

Protocol accepted and approved by:

Senior Medical Officer, Division of Clinical Development

[redacted]

Declaration of Investigator

I have read and understood all sections of the protocol entitled "Randomized, Double-Blinded, Phase 2 Study to Assess Safety and Immunogenicity of Homologous and Heterologous Prime-Boost Vaccination Strategies With Stockpiled Inactivated Monovalent Influenza A(H5) Vaccines Administered Intramuscularly With Either AS03 or MF59® as Adjuvant."

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Final Protocol Version 2.0, dated 26 February 2018, the International Council for Harmonisation harmonised tripartite guideline E6(R1): Good Clinical Practice and all applicable government regulations. I will not make changes to the protocol before consulting with BARDA or implement protocol changes without institutional review board approval except to eliminate an immediate risk to subjects. I agree to administer study treatment only to subjects under my personal supervision or the supervision of a subinvestigator.

I will not supply the investigational product to any person not authorized to receive it. Confidentiality will be protected. Subject identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from BARDA.

Signature of Principal Investigator Date

Printed Name of Principal Investigator

Table of Contents

List of Tables

List of Figures

Protocol Synopsis

Protocol Number:	BP-I-16-005
Title:	Randomized, Double-Blinded, Phase 2 Study to Assess Safety and Immunogenicity of Homologous and Heterologous Prime-Boost Vaccination Strategies With Stockpiled Inactivated Monovalent Influenza A(H5) Vaccines Administered Intramuscularly With Either AS03 or MF59® as Adjuvant
Sponsor:	Biomedical Advanced Research and Development Authority (BARDA) 200 Independence Avenue, S.W. Room 640-G Washington, DC 20201
Study Phase:	2
Study Sites:	Multiple sites in the United States
Study Population:	Approximately 720 healthy adult male or nonpregnant female subjects, 18 to 49 years old who meet all eligibility criteria
Rationale:	The main purpose of this study is to assess the ability of H5 influenza virus vaccines and adjuvants present in the National Pre-Pandemic Influenza Vaccine Stockpile (NPIVS) to generate an immune response to homologous and to antigenically distant heterologous H5 influenza virus strains. The study is designed to evaluate the safety and immunogenicity of vaccination strategies with homologous or antigenically distant heterologous H5 influenza virus vaccines administered with AS03 or MF59 adjuvant.
Objectives:	**Primary:** <u>Safety:</u> • To assess the safety and reactogenicity for 8 days postvaccination, inclusive of the vaccination day (Day 1 through Day 8 and Day 22 through Day 29), of a 2-dose vaccination series using homologous monovalent inactivated H5 influenza virus vaccine or antigenically distant heterologous H5 influenza virus vaccines administered intramuscularly (IM) with AS03 or MF59 adjuvant on Days 1 and 22 (henceforth referred to as "prime-boost"), as determined by solicited local and systemic reactogenicity symptoms.

Safety:

- To assess the safety and reactogenicity for 8 days postvaccination, inclusive of the vaccination day (Day 1 through Day 8, Day 22 through Day 29, and Day 142 through Day 149), of a 3-dose vaccination series using homologous monovalent inactivated H5 influenza virus vaccine administered IM with AS03 or MF59 adjuvant on Days 1 and 22, and a third dose 120 days after the second dose with an antigenically heterologous H5 influenza virus vaccine administered IM with AS03 or MF59 adjuvant on Day 142 (henceforth referred to as "prime-prime-boost"), as determined by solicited local and systemic reactogenicity symptoms.

Immunogenicity:

- To assess the serum hemagglutination inhibition (HAI) antibody seroprotection rate (SPR) against strains contained in the study vaccines on Day 43 of the prime-boost vaccination series administered IM with AS03 or MF59 adjuvant on Days 1 and 22.
- To assess the serum HAI antibody SPR against strains contained in the study vaccines on Day 163 of the prime-prime-boost vaccination series administered IM with AS03 or MF59 adjuvant on Days 1, 22, and 142.

Secondary:

Safety:

- To assess the occurrence of serious adverse events, medically attended adverse events (MAAEs), and potentially immune-mediated medical conditions (PIMMCs; see Appendix 2, Section 12.2) in the 12 treatment groups through 12 months after the last dose of study vaccine.
- To assess the occurrence of unsolicited adverse events for 21 days after each dose of study vaccine.

Immunogenicity:

- To assess the serum HAI antibody titers, SPRs, and seroconversion rates (SCRs) against each vaccine strain in the study through Day 142 of the prime-boost vaccination series.
- To assess the serum HAI antibody titers, SPRs, and SCRs against each vaccine strain in the study through Day 262 of the prime-prime-boost vaccination series.
- To assess the serum microneutralization (MN) antibody titers and SCRs against each vaccine strain in the study through Day 142 of the prime-boost vaccination series.
- To assess the serum MN antibody titers and SCRs against each vaccine strain in the study through Day 262 of the prime-prime-boost vaccination series.

Exploratory:

Immunogenicity**:**

- To assess peripheral antibody responses to epitopes within the influenza virus surface proteins hemagglutinin or neuraminidase induced by prime-boost or prime-prime-boost vaccination series.
- To examine cell-mediated (eg, B cell, CD4+ T cell, CD8+ T cell) responses in a subset composed of approximately half of enrolled subjects using peripheral blood mononuclear cells collected at Day 1, Day 22, Day 43, and Day 142 (Groups A-D, G-J) or Day 1, Day 22, Day 43, Day 142, Day 163, and Day 262 (Groups E, F, K, L).

Subject Population

Inclusion Criteria

Each subject must meet all of the following criteria to be enrolled in this study:

1. Is a male or nonpregnant female 18 to 49 years of age, inclusive, on Day 1 (first vaccination).
2. Will avoid nonstudy vaccinations until 21 days after the last vaccination.
3. Provides written informed consent prior to the initiation of any study-related procedures.
4. Has a stable health status, as established by physical examination, vital sign measurements, and medical history.
5. Has access to a consistent and reliable means of telephone contact, which may be in the home, workplace, or by personal mobile electronic device.
6. Is able to understand and comply with planned study procedures.
7. Lives a reasonable distance from the site to be able to travel to and from the site for follow-up visits and agrees to go to the site for evaluation in the case of an adverse event.
8. Agrees to stay in contact with the site for the duration of the study, has no current plans to move from the study area, and provides updated contact information as necessary.

Exclusion Criteria

A subject meeting any of the following criteria will be excluded from the study:

1. Has a known allergy to eggs or other components of the vaccine (including gelatin, formaldehyde, octoxinol-9, thimerosal, or chicken protein), or allergy to squalene-based adjuvants or has had severe reactions following previous immunizations with contemporary influenza virus vaccines.
2. A woman who has a positive urine pregnancy test prior to vaccination in this study or a woman who is breastfeeding.
3. A female of childbearing potential[a] who refuses to use an acceptable method of birth control[b] from Day 1 (first vaccination) to end-of-study visit and, if sexually active, who has not used a reliable birth control method for at least 2 months prior to Day 1 (first vaccination).

[a] Female of childbearing potential is defined as post-onset menarche and premenopausal female capable of becoming pregnant. This does not include females who meet any of the following conditions: menopausal >1 year, tubal ligation >1 year, bilateral salpingo-oophorectomy, or hysterectomy.

[b] Adequate contraception is defined as a contraceptive method with failure rate

of less than 1% per year when used consistently and correctly and, when applicable, in accordance with the product label, for example: abstinence from penile-vaginal intercourse; 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; male partner sterilization at least 6 months prior to the female Day 1 (first vaccination), and this male is the sole partner for that subject (The information on the male sterility can come from the site personnel's review of the subject's medical records or interview with the subject on her medical history); male condom combined with a vaginal spermicide (foam, gel, film, cream, or suppository); male condom combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, film, cream, or suppository).

4. Is immunosuppressed as a result of an underlying illness or treatment, or anticancer chemotherapy or radiation therapy (cytotoxic) within the preceding 36 months prior to Day 1 (first vaccination).
5. Has an active neoplastic disease or a history of any hematologic malignancy. A subject with superficial skin cancer who does not require intervention other than local excision is not excluded.
6. Has long-term use (≥14 consecutive days) of glucocorticoids including oral or parenteral prednisone or equivalent (>20 mg total dose per day) or high-dose inhaled steroids (>800 mcg/day of beclomethasone dipropionate or equivalent) within 1 month prior to screening. (Low-dose [≤800 mcg/day of beclomethasone dipropionate or equivalent] inhaled and topical steroids are allowed).
7. Has a diagnosis of schizophrenia, bipolar disease, or other major psychiatric diagnosis.
8. Has been hospitalized for psychiatric illness, history of suicide attempt, or confinement for danger to self or others, within the past 10 years.
9. Has a neurological or psychiatric diagnosis, which, although stable, is judged by the investigator to render the potential subject unable or unlikely to comply with the protocol or to provide accurate safety reports.
10. Has received immunoglobulin or other blood product (with the exception of Rho[D] immune globulin) within the 3 months prior to Day 1 (first vaccination).
11. Has received any live vaccine within 4 weeks or inactivated vaccines within 2 weeks prior to Day 1 (first vaccination). This includes seasonal influenza vaccines.
12. Has an acute or chronic medical condition that, in the opinion of the investigator, would render vaccination unsafe or would

interfere with the evaluation of responses. This includes PIMMCs such as Guillain-Barré syndrome, narcolepsy, current or history of autoimmune or chronic inflammatory disease (listed in Appendix 2, Section 12.2).

13. Has a first-degree relative with narcolepsy.
14. Has an acute illness, including body temperature greater than 100.4°F, at screening, immediately prior to each vaccination or, per subject report, within 3 days prior to each vaccination. Subjects with an acute illness can be rescheduled for a vaccination as long as the vaccination visit is within the visit window. Note that subjects may return for randomization following resolution of the acute illness as long as recruitment remains open and subjects are within 14 days of signing consent.
15. Has a Grade 2 or greater (by US Food and Drug Administration toxicity grade) safety laboratory value at screening.
16. Has received an experimental agent (vaccine, biologic, device, blood product, or medication) within 1 month prior to Day 1 (first vaccination) in this study or plans receipt of an experimental agent during the study period.
17. Is participating or plans to participate in another interventional clinical study (either active or follow-up phase) during the study period.
18. Has received an influenza H5 vaccine in the past or has a history of H5 influenza infection prior to enrollment.
19. Has known human immunodeficiency virus, hepatitis B, or hepatitis C infection.
20. Has a history of alcohol or drug abuse within 5 years prior to Day 1 (first vaccination).
21. Has a body mass index >35 kg/m^2.
22. Has any condition that would, in the opinion of the investigator, place him or her at an unacceptable risk of injury or render him or her unable to meet the requirements of the protocol (including site of injection reactogenicity assessments).
23. Is a first-degree relative of any person working on this study: site or sponsor.

Study Design: This is a randomized, double-blinded, Phase 2 study to assess the safety and immunogenicity of a homologous or heterologous prime-boost or prime-prime-boost series with inactivated monovalent influenza H5 vaccines stored in the NPIVS, administered IM with either AS03 or MF59 adjuvant in healthy males and nonpregnant females, aged 18 to 49 years, inclusive.

Screening will occur within a 14-day period before randomization. Approximately 720 subjects will be equally and randomly assigned to one of 12 study groups within each site and will receive either 2 doses of adjuvanted vaccine separated by 21 days (Groups A-D, G-J) or 2 doses of adjuvanted vaccine separated by 21 days followed by a third dose of adjuvanted vaccine 120 days following the second dose (Groups E, F, K, L). Approximately half of enrolled subjects per study group will be selected to provide a blood sample for peripheral blood mononuclear cell collection. Study staff not involved in IP preparation and administration will be blinded to unique group assignment until clinical study report (CSR) database freeze.

Treatment Arms

<table>
<tr><th>Study Group</th><th>Dose #1 (Day 1) Strain Details</th><th>Dose #2 (Day 22) Strain Details</th><th>Dose #3 (Day 142) Strain Details</th><th>Adjuvant</th></tr>
<tr><td>A</td><td>VN</td><td rowspan="3">gf/WA</td><td rowspan="3">N/A</td><td rowspan="6">AS03</td></tr>
<tr><td>B</td><td>IN</td></tr>
<tr><td>C</td><td>dk/BANG</td></tr>
<tr><td>D</td><td>gf/WA</td><td>IN</td></tr>
<tr><td>E</td><td>dk/BANG</td><td>dk/BANG</td><td>bhg/QL</td></tr>
<tr><td>F</td><td>gf/WA</td><td>gf/WA</td><td>bhg/QL</td></tr>
<tr><td>G</td><td>VN</td><td rowspan="3">gf/WA</td><td rowspan="3">N/A</td><td rowspan="6">MF59</td></tr>
<tr><td>H</td><td>IN</td></tr>
<tr><td>I</td><td>dk/BANG</td></tr>
<tr><td>J</td><td>gf/WA</td><td>IN</td></tr>
<tr><td>K</td><td>dk/BANG</td><td>dk/BANG</td><td>bhg/QL</td></tr>
<tr><td>L</td><td>gf/WA</td><td>gf/WA</td><td>bhg/QL</td></tr>
</table>

Note: Investigational products are abbreviated according to the following:

- VN = A/Vietnam/1203/2004 (H5N1)
- IN = A/Indonesia/05/2005 (H5N1)
- dk/BANG = A/duck/Bangladesh/19097/2013 (H5N1)
- gf/WA = A/gyrfalcon/Washington/41088-6/2014 (H5N8)
- bhg/QL = A/barheaded goose/Qinghai Lake/1A/2005 (H5N1)

	All investigational products will be prepared and administered by an unblinded staff member. The study staff observing the subject after vaccination and the subject will be blinded to the group assigned. Subjects who participate in this study will be asked to consent to be contacted with a request to participate in future clinical studies of subjects who have been vaccinated against influenza H5, such as longer interval prime-boost studies.
Estimated Study Duration:	Up to 13 months per subject for Groups A-D and G-J and up to 17 months per subject for Groups E, F, K, and L.
Safety Assessments:	Safety assessments will include the following: • Vital sign measurements (oral temperature, pulse rate, and blood pressure) • Physical examination • Clinical safety laboratory tests (hematology, coagulation, chemistry/metabolic panel, urine pregnancy in women of childbearing potential) • Solicited local and systemic reactogenicity symptoms during the 8 days after each vaccination • Adverse events through 21 days following each vaccination • Serious adverse events, MAAEs, and PIMMCs from the time of the first vaccination through approximately 12 months after the last vaccination

Immunogenicity Assessments:	Immunogenicity assessments will include the following assessments at Day 1, Day 22, Day 43, and Day 142 (Groups A-D, G-J) and at Day 1, Day 22, Day 43, Day 142, Day 163, and Day 262 (Groups E, F, K, L). • 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 prevaccination HAI titer <1:10 and a postvaccination HAI titer ≥1:40, or a prevaccination HAI titer ≥1:10 and a minimum 4-fold rise in postvaccination HAI titer • Serum MN antibody titers • Seroconversion based on serum MN antibody titers, defined as either a prevaccination MN titer <1:10 and a postvaccination MN titer ≥1:40, or a prevaccination MN titer ≥1:10 and a minimum 4-fold rise in postvaccination MN titer
Investigational Product, Dosage, and Route of Administration:	Investigational product consists of H5 influenza virus vaccine aseptically prepared with adjuvant at the site and administered IM as either 2 doses of adjuvanted vaccine 21 days apart (Groups A-D, G-J) or 2 doses of adjuvanted vaccine separated by 21 days followed by a third dose of adjuvanted vaccine 120 days following the second dose (Groups E, F, K, L). The study vaccines will be prepared by mixing H5 influenza virus vaccine antigen with either AS03 or MF59 adjuvant prior to administration. The study vaccine (0.5 mL) should be administered by IM injection in the deltoid muscle of the arm within 30 minutes of mixing. Each vaccination will be given in alternating arms whenever possible. If a subject has a scar or tattoo that interferes with injection site assessment, the vaccine can be given in the same arm as the previous injection.
Sample Size:	Approximately 720 subjects with 60 subjects per study group will be enrolled in the study.

Statistical Methods: Data will be summarized with descriptive statistics for quantitative parameters, and by incidence rates and the corresponding 95% confidence intervals for categorical findings, as appropriate.

No formal significance testing will be performed. Details of the statistical analyses, methods, and data conventions are described in the statistical analysis plan.

No formal independent data monitoring committee meetings are planned for this study. The independent data monitoring committee will meet only if a pausing rule is met.

Two interim analyses are planned based on cumulative immunogenicity and safety data after all subjects complete Day 43 and all subjects complete Day 163. At each time point, the study database will be monitored, cleaned, and frozen through the data cut time point. Safety and immunogenicity data will be summarized by study group. Interim analysis results will be unblinded at the group level, and each group will be assigned a fake name. Results will be provided to the sponsor with groups identified only by their fake names. A single CSR will be written with unblinded data at the subject level after Groups E, F, K, L have completed Day 262. Additional safety results from the time of CSR database freeze until the end-of-study visit for all groups will be included in an addendum to the final CSR.

Date of Protocol: 26 February 2018

List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BARDA	Biomedical Advanced Research and Development Authority
CDROM	Compact Disc Read-Only Memory
CFR	Code of Federal Regulations
CI	confidence interval
CSR	clinical study report
eCRF	electronic case report form
FAS	full analysis set
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
HA	hemagglutinin
HAI	hemagglutination inhibition
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
IFAS	immunogenicity-full analysis set
IM	intramuscularly
IP	investigational product
IPPS	immunogenicity per-protocol set
IRB	institutional review board
IRT	interactive response technology
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MN	microneutralization
NPIVS	National Pre-Pandemic Influenza Vaccine Stockpile
PBMC	peripheral blood mononuclear cell
PIMMC	potentially immune-mediated medical condition
PT	preferred term
SAE	serious adverse event

Abbreviation	Definition
SCR	seroconversion rate
SOC	system organ class
SPR	seroprotection rate
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal

1 Introduction

Avian influenza H5N1 virus infections were first detected in humans in 1997 during a poultry outbreak in Hong Kong SAR, China. Since its re-emergence in 2003, influenza H5N1 virus has spread from Asia to Europe, Africa, and North America, becoming endemic in poultry in some countries in Asia and Africa. Reports of sporadic transmission from birds to humans continue, and as of July 2017, 859 individuals have been diagnosed with H5N1 virus infection, including 453 deaths. Antigenic drift has resulted in over 40 distinct H5 hemagglutinin (HA) clades since 1997, and live-bird market surveillance identified novel clade 2.3.4.4 reassortant viruses of different subtypes in Asia since 2009, including H5N2, H5N3, H5N5, H5N6, and H5N8 strains (Gu et al 2011; Zhao et al 2012; Zhao et al 2013; Hill et al 2015; Wong et al 2015;World Health Organization 2017a). Some of these clade 2.3.4.4 viruses have begun to spread internationally to Asia (H5N6), Europe, Africa, and North America (H5N8). After the first detection of the Eurasian H5N8 in the Pacific Northwest of the United States in December 2014, the resulting reassortant H5N2 viruses spread to 21 states by June 2015 affecting 48 million poultry (United States Department of Agriculture 2016). No human cases of H5N8 were detected; however, there have been 16 laboratory-confirmed cases of human infection with H5N6 (clade 2.3.4.4) reported in China since 2014, including 9 fatalities (World Health Organization 2017b).

While the risk of human infection with H5 influenza viruses is low, the Department of Health and Human Services continuously monitors the risk and prepares to respond to the threat of novel influenza virus outbreaks in the United States. In order to prepare and respond effectively to future influenza pandemic threats, the Biomedical Advanced Research and Development Authority (BARDA) within the Office of the Assistant Secretary for Preparedness and Response, has established and maintains the National Pre-Pandemic Influenza Vaccine Stockpile (NPIVS) that comprises bulk adjuvants, pre-pandemic antigens, and final containers of vaccines that were manufactured from candidate vaccine viruses from representative clades of H5 influenza viruses (eg, clades 1, 2.1, 2.2, 2.3). These candidate vaccine viruses are carefully chosen based on ongoing surveillance of influenza A viruses circulating in animals and assessment of associated potential pandemic risk.

In the case of a declared pandemic emergency, the vaccine exactly matching the antigenic properties of the pandemic virus will not be available until several months later. Production issues, such as virus and purification yields that vary depending on the virus characteristics,

make it difficult to estimate how long it would take during a pandemic emergency to produce enough doses of any vaccine to protect the US population. Therefore, it is important to develop potential strategies for immediate deployment of stockpiled H5 influenza virus vaccines as an interim intervention in response to a pandemic emergency. Previous studies suggest that heterologous prime and boost vaccination regimens (ie, different HA antigens used for prime and boost vaccinations) may be superior to homologous prime and boost vaccination regimens (ie, the same HA antigens used for prime and boost vaccinations) in generating cross-reactive immune responses to antigenically divergent influenza viruses (Belshe et al 2011, Belshe et al 2014, Gillard et al 2013, Gillard et al 2014, Leroux-Roels et al 2010, Levine et al 2017). Furthermore, there is some evidence suggesting that when compared to a homologous prime-boost vaccination regimen, a heterologous prime-boost vaccination regimen including adjuvant may broaden and enhance cross-reactive hemagglutination inhibition (HAI) antibody responses to a panel of antigenically divergent H5 influenza viruses (Levine et al 2017, unpublished data).

Influenza virus vaccines induce antibodies against the viral HA antigen in the vaccine, thereby blocking viral attachment to human respiratory epithelial cells. In some human challenge studies of other influenza viruses, antibody titers of at least 1:40 have been associated with protection from influenza infection in up to 50% of subjects.

Sanofi Pasteur Influenza A/Vietnam/1203/2004 (H5N1), A/Indonesia/05/2005 (H5N1), and A/bar-headed goose/Qinghai Lake/1A/2005 (H5N1) vaccines contain 30 mcg/mL HA from SJRG-161052, Indo5/PR8-RG2, and SJRG-163222 candidate vaccine viruses respectively, in sodium phosphate buffered isotonic saline. These monovalent vaccines also contain gelatin (0.05%), trace amounts of formaldehyde (≤200 mcg/mL), polyethylene glycol p-isooctylphenyl ether (≤0.05%), and sucrose (≤2.0%). In addition, thimerosal at a concentration of approximately 0.01% was added as a preservative (Fluzone Quadrivalent [Influenza Vaccine] 2016).

Seqirus (formerly Novartis) A/duck/Bangladesh/19097/2013 H5N1 vaccine contains 30 mcg/mL HA from SJ007 candidate vaccine virus in sodium phosphate buffered isotonic saline. Each 0.5 mL vial of monovalent vaccine may also contain residual amounts of Madin Darby canine kidney cell protein (≤8.4 mcg), protein other than HA (≤160 mcg), Madin Darby canine kidney cell DNA (≤10 ng), polysorbate 80 (≤1500 mcg),

cetyltrimethylammonium bromide (≤18 mcg), and β–propiolactone (≤0.5 mg) (Flucelvax Quadrivalent [Influenza Vaccine] 2016).

Seqirus (formerly bioCSL) A/gyrfalcon/Washington/41088-6/2014 (H5N8) vaccine contains 30 mcg/mL HA from IDCDC-RG43A candidate vaccine virus in isotonic phosphate buffer. Each 0.5 mL vial of monovalent vaccine may also contain trace amounts of sodium taurodeoxycholate (≤10 ppm), ovalbumin (<1 mcg), neomycin sulfate (≤0.2 pg), polymyxin B (≤0.03 pg), and beta-propiolactone (≤25 ng) (Afluria 2010).

The adjuvant MF59® is an oil-in-water emulsion composed of squalene and a buffer; the emulsion is stabilized by the addition of 2 emulsifiers (a water-soluble surfactant [polysorbate 80, also known as Tween® 80] and an oil-soluble surfactant [sorbitan trioleate, also known as Span® 85]). Biodegradable squalene oil is a natural metabolite of cholesterol and a normal component of cell membranes. MF59 enhances immune responses to antigen by targeting 3 different cell types, including monocytes, macrophages, and granulocytes. MF59 has a range of effects on these cells, including increased antigen uptake, release of chemoattractants, and induction of cell differentiation (FLUAD [Influenza Vaccine, Adjuvanted] 2016).

MF59 has been developed to enhance the immunogenicity of purified subunit antigens, has been tested in several animal models in combination with different antigens, and has been evaluated in humans (Schultze et al 2008). MF59 was the first adjuvant for human use to be licensed after alum and, as part of an enhanced seasonal trivalent inactivated subunit influenza vaccine (FLUAD®) for the elderly, is now licensed in more than 30 countries worldwide. MF59 is also the adjuvant of European Union-licensed monovalent A(H1N1) swine influenza subunit egg-derived vaccine (FOCETRIA®), a cell-derived pandemic vaccine (CELTURA®), and licensed pre-pandemic vaccine (AFLUNOV®).

Warnings and precautions for the influenza virus vaccines include history of a hypersensitivity reaction to chicken or egg proteins or life-threatening reactions to previous influenza vaccinations. Immunocompromised persons may have a reduced immune response to influenza virus vaccines. The most common (≥10%) adverse reactions observed with the vaccines used in this study are pain at injection site, tenderness, headache, malaise, induration/swelling, redness, itching, myalgia, arthralgia, shivering, and sweating.

Extensive safety data have been gathered on the use of glycoprotein antigens or recombinant proteins combined with MF59. These data indicate that such vaccine antigens, when administered with MF59, are safe, and generally well tolerated. Additionally, these vaccines have frequently elicited a strong antibody response against the particular antigens. As of 30 April 2015, approximately 43 600 subjects had received at least 1 dose of influenza virus vaccines combined with MF59 adjuvant in completed clinical studies. The completed studies showed that the MF59 adjuvant significantly improved the immunogenicity of inactivated subunit influenza virus vaccines, with a clinically acceptable increase in the incidence of injection site reactions (Schultze et al 2008). According to an integrated safety analysis, filed in the BB-Master File for MF59, there was an increased risk of solicited local and systemic reactions in subjects exposed to MF59, while there was a similar or decreased risk of all unsolicited adverse events (AEs), autoimmune diseases, new onset chronic diseases, cardiovascular disease, serious adverse events (SAEs), hospitalizations, and deaths when compared with non-MF59-adjvuanted vaccines (Pellegrini et al 2009).

The AS03 adjuvant is composed of squalene, DL-α-tocopherol, and polysorbate 80. AS03 is approved for human use as the adjuvant component of the Influenza H5N1 Virus Monovalent Vaccine, Adjuvanted (Influenza A (H5N1) Virus Monovalent Vaccine 2013).

Other influenza vaccines containing AS03 adjuvant were administered outside the United States during the Influenza A 2009 (H1N1) pandemic. The following AEs were identified: anaphylaxis, allergic reactions, febrile convulsions, Guillain-Barre syndrome, narcolepsy, somnolence, paresthesia, angioedema, generalized skin reactions, urticaria, and injection site reactions (including inflammation, mass, necrosis, and ulcer) (Influenza A (H5N1) Virus Monovalent Vaccine 2013).

Both the AS03 and MF59-adjuvanted vaccines have been licensed in the United States (eg, AS03 in the Influenza A [H5N1] Virus Monovalent Vaccine, Adjuvanted [Influenza A (H5N1) Virus Monovalent Vaccine 2013] and MF59 in the FLUAD vaccine [FLUAD (Influenza Vaccine, Adjuvanted) 2016]). There are no major safety concerns associated with the use of these adjuvants; 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 subjects who received adjuvanted vaccine; however, narcolepsy developed almost exclusively in the pediatric population vaccinated with influenza A(H1N1) adjuvanted with

AS03 (Pandemrix®, GlaxoSmithKline, Wavre, Belgium, produced in Dresden, Germany) and primarily in Scandinavian countries (Lind et al 2014, Nohynek et al 2012). A small study to assess the risk of narcolepsy following administration of a similar vaccine adjuvanted with AS03 (Arepanrix®, GlaxoSmithKline, Wavre, Belgium, produced in Quebec City, Canada) was performed in Quebec, Canada (Montplaisir et al 2014). The Canadian study showed a small risk of developing narcolepsy after receiving the AS03-adjuvanted A(H1N1)pdm09 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. An additional study was conducted in the United States, which found that influenza vaccines containing the A(H1N1)pdm09 virus strain were not associated with an increased risk of narcolepsy (Duffy et al 2014). Finally, the "SOMNIA study" conducted by the US Centers for Disease Control and Prevention assessed the risk of narcolepsy following administration of adjuvanted A(H1N1)pdm09 vaccines. Comparison of incidence rates of narcolepsy before, during, and after the use of adjuvanted A(H1N1)pdm09 influenza vaccines provided no evidence outside of the signaling country Sweden (Shimabukuro et al 2017).

This is a randomized, double-blinded, Phase 2 study to assess the safety and immunogenicity of a homologous or heterologous vaccination series with inactivated monovalent influenza H5 vaccines stored in the NPIVS, administered intramuscularly (IM) with either AS03 or MF59 adjuvant in healthy males and nonpregnant females, aged 18 to 49 years, inclusive. Two doses of adjuvanted vaccine separated by 21 days or 2 doses of adjuvanted vaccine separated by 21 days followed by a third dose of adjuvanted vaccine 120 days following the second dose will utilize HA antigens from the NPIVS.

The study is designed to further inform options for strategic deployment of pre-pandemic influenza vaccines stockpiled in the NPIVS. In particular, we will determine whether 1) the antigenic characteristics of 2 antigens used for prime and boost and 2) the sequence in which the priming and boosting antigens are administered are important for optimal elicitation of immune responses to the vaccine. The antigens included in this study were carefully chosen based on the relative antigenic distance between the HAs of pre-pandemic vaccine strains and relative to the currently circulating H5 influenza viruses. Furthermore, this study will address serologic responses to the vaccination regimens when administered with each of the adjuvants (AS03 or MF59) held in the NPIVS and whether boosting can be observed with heterologously distinct strains when using either adjuvant (AS03 or MF59) in a single-dose or a 2-dose priming series.

2 Study Objectives

2.1 Primary Objectives

2.1.1 Primary Safety Objective

- To assess the safety and reactogenicity for 8 days postvaccination, inclusive of the vaccination day (Day 1 through Day 8 and Day 22 through Day 29), of a 2-dose vaccination series using homologous monovalent inactivated H5 influenza virus vaccine or antigenically distant heterologous H5 influenza virus vaccines administered IM with AS03 or MF59 adjuvant on Days 1 and 22 (henceforth referred to as "prime-boost"), as determined by solicited local and systemic reactogenicity symptoms.
- To assess the safety and reactogenicity for 8 days postvaccination, inclusive of the vaccination day (Day 1 through Day 8, Day 22 through Day 29, and Day 142 through Day 149), of a 3-dose vaccination series using homologous monovalent inactivated H5 influenza virus vaccine administered IM with AS03 or MF59 adjuvant on Days 1 and 22, and a third dose 120 days after the second dose with an antigenically heterologous H5 influenza virus vaccine administered IM with AS03 or MF59 adjuvant on Day 142 (henceforth referred to as "prime-prime-boost"), as determined by solicited local and systemic reactogenicity symptoms.

2.1.2 Primary Immunogenicity Objective

- To assess the serum HAI antibody seroprotection rate (SPR) against strains contained in the study vaccines on Day 43 of the prime-boost vaccination series administered IM with AS03 or MF59 adjuvant on Days 1 and 22.
- To assess the serum HAI antibody SPR against strains contained in the study vaccines on Day 163 of the prime-prime-boost vaccination series administered IM with AS03 or MF59 adjuvant on Days 1, 22, and 142.

2.2 Secondary Objectives

2.2.1 Secondary Safety Objectives

- To assess the occurrence of SAEs, medically attended adverse events (MAAEs), and potentially immune-mediated medical conditions (PIMMCs; see Appendix 2, Section 12.2) in the 12 treatment groups through 12 months after the last dose of study vaccine.
- To assess the occurrence of unsolicited AEs for 21 days after each dose of study vaccine.

2.2.2 Secondary Immunogenicity Objectives

- To assess the serum HAI antibody titers, SPRs, and seroconversion rates (SCRs) against each vaccine strain in the study through Day 142 of the prime-boost vaccination series.
- To assess the serum HAI antibody titers, SPRs, and SCRs against each vaccine strain in the study through Day 262 of the prime-prime-boost vaccination series.
- To assess the serum microneutralization (MN) antibody titers and SCRs against each vaccine strain in the study through Day 142 of the prime-boost vaccination series.
- To assess the serum MN antibody titers and SCRs against each vaccine strain in the study through Day 262 of the prime-prime-boost vaccination series.

2.3 Exploratory Immunogenicity Objectives

- To assess peripheral antibody responses to epitopes within the influenza virus surface proteins HA or neuraminidase induced by prime-boost or prime-prime-boost vaccination series.
- To examine cell-mediated (eg, B cell, CD4+ T cell, CD8+ T cell) responses in a subset composed of approximately half of enrolled subjects using peripheral blood mononuclear cells (PBMCs) collected at Day 1, Day 22, Day 43, and Day 142 (Groups A-D, G-J) or Day 1, Day 22, Day 43, Day 142, Day 163, and Day 262 (Groups E, F, K, L).

3 Investigational Plan

3.1 Study Design

This is a randomized, double-blinded, Phase 2 study to assess the safety and immunogenicity of a homologous or heterologous prime-boost or prime-prime-boost series with inactivated monovalent influenza H5 vaccines stored in the NPIVS, administered IM with either AS03 or MF59 adjuvant in healthy males and nonpregnant females, aged 18 to 49 years, inclusive.

Screening will occur within a 14-day period before randomization. Approximately 720 subjects will be equally and randomly assigned to one of 12 study groups within each site. Study staff not involved in investigational product (IP) preparation and administration will be blinded to unique group assignment. Two doses of adjuvanted vaccine separated by 21 days (Groups A-D, G-J) or 2 doses of adjuvanted vaccine separated by 21 days followed by a third dose of adjuvanted vaccine 120 days following the second dose (Groups E, F, K, L) will include HA antigen from the NPIVS.

Investigational product treatment arms are detailed in Table 3–1.

Table 3–1 Treatment Arms

Study Group	Dose #1 (Day 1) Strain Details (Manufacturer)	Dose #2 (Day 22) Strain Details (Manufacturer)	Dose #3 (Day 142) Strain Details (Manufacturer)	Adjuvant
A	A/Vietnam/1203/2004 H5N1 (Sanofi Pasteur)	A/gyrfalcon/Washington/41088-6/2014 H5N8 (Seqirus)	N/A	AS03
B	A/Indonesia/05/2005 H5N1 (Sanofi Pasteur)			
C	A/duck/Bangladesh/19097/2013 H5N1 (Seqirus)			
D	A/gyrfalcon/Washington/41088-6/2014 H5N8 (Seqirus)	A/Indonesia/05/2005 H5N1 (Sanofi Pasteur)		
E	A/duck/Bangladesh/19097/2013 H5N1 (Seqirus)	A/duck/Bangladesh/19097/2013 H5N1 (Seqirus)	A/barheaded goose/Qinghai Lake/1A/2005 (H5N1) (Sanofi Pasteur)	
F	A/gyrfalcon/Washington/41088-6/2014 H5N8 (Seqirus)	A/gyrfalcon/Washington/41088-6/2014 H5N8 (Seqirus)	A/barheaded goose/Qinghai Lake/1A/2005 (H5N1) (Sanofi Pasteur)	
G	A/Vietnam/1203/2004 H5N1 (Sanofi Pasteur)	A/gyrfalcon/Washington/41088-6/2014 H5N8 (Seqirus)	N/A	MF59
H	A/Indonesia/05/2005 H5N1 (Sanofi Pasteur)			
I	A/duck/Bangladesh/19097/2013 H5N1 (Seqirus)			
J	A/gyrfalcon/Washington/41088-6/2014 H5N8 (Seqirus)	A/Indonesia/05/2005 H5N1 (Sanofi Pasteur)		
K	A/duck/Bangladesh/19097/2013 H5N1 (Seqirus)	A/duck/Bangladesh/19097/2013 H5N1 (Seqirus)	A/barheaded goose/Qinghai Lake/1A/2005 (H5N1) (Sanofi Pasteur)	
L	A/gyrfalcon/Washington/41088-6/2014 H5N8 (Seqirus)	A/gyrfalcon/Washington/41088-6/2014 H5N8 (Seqirus)	A/barheaded goose/Qinghai Lake/1A/2005 (H5N1) (Sanofi Pasteur)	

Abbreviation: N/A, not applicable.

All IP will be prepared and administered by an unblinded staff member. The study staff observing the subject after vaccination and the subject will be blinded to group assigned.

Subject completion is defined as completing all study visits through Visit 9 (end-of-study visit) for Groups A-D and G-J (Table 12–1) or Visit 14 (end-of-study visit) for Groups E, F, K, L (Table 12–2). Approximately half of enrolled subjects per study group will be selected to provide a blood sample for PBMC collection. A select number of sites will have capability for PBMC collections, and only subjects enrolled at those sites will contribute to the PBMC subset. Subjects who participate in this study will be asked to consent to be contacted with a request to participate in future clinical studies of subjects who have been vaccinated against influenza H5, such as longer interval prime-boost studies.

No formal independent data monitoring committee (IDMC) meetings are planned for this study. The IDMC will meet only if a pausing rule is met.

Two interim analyses are planned based on cumulative immunogenicity and safety data after all subjects complete Day 43 and all subjects complete Day 163. At each time point, the study database will be monitored, cleaned, and frozen through the data cut time point. Safety and immunogenicity data will be summarized by study group. Interim analysis results will be unblinded at the group level, and each group will be assigned a fake name. Results will be provided to the sponsor with groups identified only by their fake names.

A single clinical study report (CSR) will be written with unblinded data at the subject level after Groups E, F, K, L have completed Day 262. Additional safety results from the time of CSR database freeze until the end-of-study visit for all groups will be included in an addendum to the final CSR.

3.1.1 Rationale of Study Design

The main purpose of this study is to assess the ability of H5 influenza vaccines and adjuvants present in the NPIVS to generate an immune response to homologous and to antigenically distant heterologous H5 influenza virus strains.

The study is designed to evaluate the safety and immunogenicity of vaccination strategies with homologous or antigenically distant heterologous H5 influenza virus vaccines administered with AS03 or MF59 adjuvant.

3.1.2 Study Groups

There will be a total of 12 study groups. For a complete list of study groups and corresponding vaccination and adjuvants schemes refer to Table 3–1.

3.1.3 Study Pausing Rules

Study pausing rules will be monitored throughout the study by the medical monitor. The sponsor will pause study enrollment and study vaccine administration and the IDMC will review unblinded safety data if any of the following are met:

- Occurrence of one or more SAE(s), MAAE(s), or PIMMC(s) judged to be related to IP; OR
- Any potentially life-threatening AE judged to be related to IP (An AE or suspected adverse reaction is considered “life threatening” if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death); OR
- A death, if judged to be related to IP; OR
- Anaphylaxis or bronchospasm within 4 hours of injection judged to be related to IP; OR
- 10% of vaccinated subjects at a given vaccination time point when at least 50% of subjects in that group have been vaccinated experience the same or similar systemic or local Grade 3 (toxicity scoring) or higher event; OR
- A pattern of significant symptoms, physical findings, or laboratory abnormalities that, although individually minor, collectively represent a safety concern in the opinion of the investigator or the medical monitor.

3.1.4 Future Investigations

Using the informed consent form (ICF), subjects who participate in this study will also be asked the following questions:

1. Permission to be contacted with a request to participate in future clinical studies of subjects who have been vaccinated against influenza H5, such as longer interval prime-boost studies.
2. Permission to obtain and store an additional aliquot of serum and to obtain and store any leftover serum from research laboratories for future investigations, such as testing for immune response to heterologous influenza H5 or other strains or subtypes of influenza viruses.

4 Subject Selection and Withdrawal Criteria

4.1 Selection of Study Population

Approximately 720 subjects will be enrolled at multiple sites in the United States. Subjects will be assigned to study treatment only if they meet all of the inclusion criteria and none of the exclusion criteria.

Deviations from the inclusion and exclusion criteria are not allowed. Adherence to the criteria as specified in the protocol is essential. Subjects must satisfy all of the following criteria at study entry and eligibility must be reviewed just prior to each vaccination.

4.1.1 Inclusion Criteria

Each subject must meet all of the following criteria to be enrolled in this study:

1. Is a male or nonpregnant female 18 to 49 years of age, inclusive, on Day 1 (first vaccination).
2. Will avoid nonstudy vaccinations until 21 days after the last vaccination.
3. Provides written informed consent prior to the initiation of any study-related procedures.
4. Has a stable health status, as established by physical examination, vital sign measurements, and medical history.
5. Has access to a consistent and reliable means of telephone contact, which may be in the home, workplace, or by personal mobile electronic device.
6. Is able to understand and comply with planned study procedures.
7. Lives a reasonable distance from the site to be able to travel to and from the site for follow-up visits and agrees to go to the site for evaluation in the case of an AE.
8. Agrees to stay in contact with the site for the duration of the study, has no current plans to move from the study area, and provides updated contact information as necessary.

4.1.2 Exclusion Criteria

A subject meeting any of the following criteria will be excluded from the study:

1. Has a known allergy to eggs or other components of the vaccine (including gelatin, formaldehyde, octoxinol-9, thimerosal, or chicken protein), or allergy to squalene-based adjuvants or has had severe reactions following previous immunizations with contemporary influenza virus vaccines.
2. A woman who has a positive urine pregnancy test prior to vaccination in this study or a woman who is breastfeeding.
3. A female of childbearing potential[a] who refuses to use an acceptable method of birth control[b] from Day 1 (first vaccination) to end-of-study visit and, if sexually active, who has not used a reliable birth control method for at least 2 months prior to Day 1 (first vaccination).

[a] Female of childbearing potential is defined as post-onset menarche and premenopausal female capable of becoming pregnant. This does not include females who meet any of the following conditions: menopausal >1 year, tubal ligation >1 year, bilateral salpingo-oophorectomy, or hysterectomy.

[b] Adequate contraception is defined as a contraceptive method with failure rate of less than 1% per year when used consistently and correctly and, when applicable, in accordance with the product label, for example: abstinence from penile-vaginal intercourse; 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; male partner sterilization at least 6 months prior to the female Day 1 (first vaccination), and this male is the sole partner for that subject (The information on the male sterility can come from the site personnel's review of the subject's medical records or interview with the subject on her medical history); male condom combined with a vaginal spermicide (foam, gel, film, cream, or suppository); male condom combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, film, cream, or suppository).

4. Is immunosuppressed as a result of an underlying illness or treatment, or anticancer chemotherapy or radiation therapy (cytotoxic) within the preceding 36 months prior to Day 1 (first vaccination).
5. Has an active neoplastic disease or a history of any hematologic malignancy. A subject with superficial skin cancer who does not require intervention other than local excision is not excluded.

6. Has long-term use (≥14 consecutive days) of glucocorticoids including oral or parenteral prednisone or equivalent (>20 mg total dose per day) or high-dose inhaled steroids (>800 mcg/day of beclomethasone dipropionate or equivalent) within 1 month prior to screening. (Low-dose [≤800 mcg/day of beclomethasone dipropionate or equivalent] inhaled and topical steroids are allowed).
7. Has a diagnosis of schizophrenia, bipolar disease, or other major psychiatric diagnosis.
8. Has been hospitalized for psychiatric illness, history of suicide attempt, or confinement for danger to self or others, within the past 10 years.
9. Has a neurological or psychiatric diagnosis, which, although stable, is judged by the investigator to render the potential subject unable or unlikely to comply with the protocol or to provide accurate safety reports.
10. Has received immunoglobulin or other blood product (with the exception of Rho[D] immune globulin) within the 3 months prior to Day 1 (first vaccination).
11. Has received any live vaccine within 4 weeks or inactivated vaccines within 2 weeks prior to Day 1 (first vaccination). This includes seasonal influenza vaccines.
12. Has an acute or chronic medical condition that, in the opinion of the investigator, would render vaccination unsafe or would interfere with the evaluation of responses. This includes PIMMCs such as Guillain-Barré syndrome, narcolepsy, current or history of autoimmune or chronic inflammatory disease (listed in Appendix 2, Section 12.2).
13. Has a first-degree relative with narcolepsy.
14. Has an acute illness, including body temperature greater than 100.4°F, at screening, immediately prior to each vaccination or, per subject report, within 3 days prior to each vaccination. Subjects with an acute illness can be rescheduled for vaccination as long as the vaccination visit is within the visit window. Note that subjects may return for randomization following resolution of the acute illness as long as recruitment remains open and subjects are within 14 days of signing consent.
15. Has a Grade 2 or greater (by US Food and Drug Administration [FDA] toxicity grade) safety laboratory value at screening.

16. Has received an experimental agent (vaccine, biologic, device, blood product, or medication) within 1 month prior to Day 1 (first vaccination) in this study or plans receipt of an experimental agent during the study period.
17. Is participating or plans to participate in another interventional clinical study (either active or follow-up phase) during the study period.
18. Has received an influenza H5 vaccine in the past or has a history of H5 influenza infection prior to enrollment.
19. Has known human immunodeficiency virus, hepatitis B, or hepatitis C infection.
20. Has a history of alcohol or drug abuse within 5 years prior to Day 1 (first vaccination).
21. Has a body mass index >35 kg/m^2.
22. Has any condition that would, in the opinion of the investigator, place him or her at an unacceptable risk of injury or render him or her unable to meet the requirements of the protocol (including site of injection reactogenicity assessments).
23. Is a first-degree relative of any person working on this study: site or sponsor.

4.2 Withdrawal of Subjects From the Study

The duration of the study is defined for each subject as beginning on the date signed written informed consent is provided through the last follow-up visit (Visit 9 [end-of-study visit] for Groups A-D and G-J [Table 12–1] and Visit 14 [end-of-study visit] for Groups E, F, K, L [Table 12–2]).

4.2.1 Reasons for Withdrawal/Discontinuation

Subjects may withdraw from the study or study treatment (ie, no longer receive IP) at any time and for any reason without prejudice to their future medical care by the investigator or at the site. Every effort should be made to keep subjects in the study. Refer to Section 4.2.2 for handling of withdrawals. The reasons for subjects not completing the study will be recorded. A subject may be withdrawn from the study or study treatment (ie, no longer receive IP) for any of the following reasons:

1. Does not meet the protocol inclusion or exclusion criteria at the time of the second or, if applicable, third vaccination.

2. Noncompliance with the protocol.
3. Serious or intolerable AE(s) that in the investigator's opinion requires withdrawal from the study.
4. A serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation that is Grade 2 (moderate) or greater based on FDA toxicity grading (ie, ≥2.6 × upper limit of normal [ULN]; see Appendix 3, Section 12.3) that does not resolve on repeat testing to the screening baseline value (eg, baseline toxicity score). (Note, subjects with elevated ALT and/or AST values cannot be revaccinated until resolution occurs [see Section 4.3].)
5. Other laboratory safety assessments that reveal Grade ≥3 hematological or biochemical values.
6. Symptoms or an intercurrent illness not consistent with the protocol requirements or that justifies withdrawal.
7. Lost to follow-up.
8. Other (eg, pregnancy, development of contraindications to use of IP).
9. The subject withdraws consent or the investigator or BARDA decides to discontinue the subject's participation in the study.

In addition, Study Pausing Rules (Section 3.1.3) will be monitored throughout the study by the medical monitor.

The investigator will also withdraw all subjects if BARDA terminates the study. Upon occurrence of a serious or intolerable AE, the investigator will confer with BARDA. If a subject is discontinued from the study or study treatment because of an AE, the event will be followed until it is resolved or becomes stable. Any subject may withdraw his or her consent at any time.

4.2.2 Handling of Withdrawals

Subjects are free to withdraw from the study or study treatment at any time upon request. Subject participation in the study may be stopped at any time at the discretion of the investigator or at BARDA's request.

Subjects who discontinue study treatment or active participation in the study will no longer receive IP. When a subject withdraws from the study, the reason(s) for withdrawal shall be recorded by the investigator on the relevant page of the electronic case report form (eCRF).

Whenever possible, all subjects who discontinue from the study prematurely will undergo all early termination assessments (Table 12–1 and Table 12–2). Subjects who discontinue study treatment prematurely will be encouraged to attend subsequent visits according to the protocol. Subjects who fail to return for final assessments will be contacted by the site in an attempt to have them comply with the protocol. A subject will not be considered lost to follow-up until every attempt to contact the subject has been made, at minimum 2 (documented) phone calls, followed by a registered letter. Every effort should be made to collect safety data on subjects through the end-of-study visit.

It is vital to obtain follow-up data on any subject withdrawn from the study or study treatment (ie, no longer receiving IP) because of an AE or SAE. In every case, efforts must be made to undertake protocol-specified safety follow-up procedures.

4.2.3 Replacements

If a subject is randomly assigned to a study group but not administered the first dose of IP, then a replacement subject will be randomly assigned to treatment via interactive response technology (IRT). A unique randomization number will be assigned to the replacement subject. If a subject is withdrawn from the study after receipt of the first dose of IP, this subject will not be replaced.

4.3 Revaccination Eligibility

Subjects are free to withdraw from further study vaccination at any time upon request. A subject may not be eligible to receive further study vaccination for any of the following reasons:

1. Does not meet the protocol inclusion or exclusion criteria at the time of the second or, if applicable, third vaccination.
2. Noncompliance with the protocol.
3. Serious or intolerable AE(s) that in the investigator's opinion precludes further study vaccination.

4. A serum ALT or AST elevation that is Grade 2 (moderate) or greater based on FDA toxicity grading (ie, ≥2.6 × ULN; see Appendix 3, Section 12.3) regardless of investigator-assessed clinical significance. Note, such an elevated ALT and/or AST value must be resolved on repeat testing to the screening baseline value (eg, baseline toxicity score) before revaccination can occur. Only those subjects who have resolution of the ALT and/or AST elevations within the visit window are eligible for revaccination.
5. Other laboratory safety assessments that remain clinically significant prior to planned vaccination.
6. Symptoms or an intercurrent illness not consistent with the protocol requirements or that justifies no further study vaccination.
7. Other (eg, pregnancy, development of contraindications precluding further study vaccination).

All subjects who discontinue from study treatment prematurely will follow the same visit schedule as other subjects.

5 Study Groups

5.1 Method of Assigning Subjects to Treatment Groups

Subjects will be randomly assigned to 1 of 12 study groups stratified by site. An IRT will be used to administer the randomization schedule centrally. Biostatistics will generate the randomization schedule using SAS® software Version 9.3 or later (SAS Institute Inc, Cary, North Carolina) for IRT, which will link sequential subject randomization numbers to treatment codes. The randomization schedule will be created by the dedicated randomization team, stored in a separate project area, and will be blinded to the project team.

5.2 Investigational Product Administered

All IP will be aseptically prepared and administered by an unblinded staff member, according to the details outlined in the Study Procedures Manual. The study staff observing the subject after vaccination and the subject will be blinded. Two doses of adjuvanted vaccine separated by 21 days (Groups A-D, G-J) or 2 doses of adjuvanted vaccine separated by 21 days followed by a third dose of adjuvanted vaccine 120 days following the second dose (Groups E, F, K, L), which include HA antigen from the NPIVS, will be administered IM according to Table 3–1.

The study vaccines will be prepared by mixing H5 influenza virus vaccine antigen with either AS03 or MF59 adjuvant prior to administration. The study vaccine (0.5 mL) should be administered by IM injection in the deltoid muscle of the arm within 30 minutes of mixing. Each vaccination will be given in alternating arms whenever possible. If a subject has a scar or tattoo that interferes with injection site assessment, the vaccine can be given in the same arm as the previous injection.

5.3 Management of Clinical Supplies

5.3.1 Investigational Product Packaging and Storage

Investigational product will be packaged and labelled according to applicable local and regulatory requirements. Each kit will contain a (randomized) dosage for 1 subject and will contain a sufficient quantity for dispensing for 1-time usage. Single-use vials will be labelled with a single panel label. Each kit will also be labelled with a single panel label.

Vaccine and adjuvant must be stored in a secure area (eg, 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 (35°F-46°F).

5.3.2 Investigational Product Accountability

The investigator will maintain accurate records of receipt of all IP, including dates of receipt. In addition, accurate records will be kept regarding when and how much IP is dispensed and administered to each subject in the study. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding accountability, all IP will be reconciled and retained or destroyed according to applicable regulations. No IP will be destroyed until authorized in writing by the sponsor.

5.3.3 Other Supplies

Other clinical supplies that will be provided to the sites for distribution to subjects include diary cards, a measuring tool for measuring injection site erythema and swelling, and a thermometer for measuring body temperature.

5.4 Overdose Management

An overdose is any dose of study treatment given to a subject or taken by a subject that exceeds the dose described in the protocol. Any overdose, with or without associated AEs, must be promptly reported to the SAE hotline (Section 6.2.5.4). In case of any AEs associated with the overdose, these should be reported on relevant AE/SAE sections in the eCRF. Any overdose should be recorded as a protocol violation and promptly reported to the sponsor. No overdoses are expected as the vaccine and adjuvant will be administered by study staff.

5.4.1 Treatment of Overdose

Treatment of overdose would include supportive and symptomatic care, according to the standards of care at the site. The investigator should promptly notify the medical monitor about the overdose and seek his/her input on the medical management, as needed.

5.5 Blinding

This is a double-blind study. All IP will be prepared and administered by an unblinded study staff member. Investigational product accountability will be monitored by a separate unblinded monitor. All other persons involved in the study will be blinded to study group assignment, including the study staff observing the subject after vaccination and the subject. Until the final database lock and unblinding, all unblinded data analyses will be handled by the unblinded team of statisticians and programmers. A strict firewall between the blinded and unblinded teams will be maintained.

For the 2 planned interim analyses, BARDA, site personnel, and subjects will be unblinded for all interim data at Day 43 and Day 163 only at the study group level (ie, data will be provided with each group having a fake designation). For the final analysis, all parties will be unblinded to all data at the subject level at Day 142 (Groups A-D, G-J) and Day 262 (Groups E, F, K, L).

With the exception of the unblinded study staff who administer the IP and a separate unblinded monitor who will monitor IP accountability, all other study staff are to remain blinded until CSR database freeze and a formal unblinding is scheduled. The members of the IDMC will review subject level unblinded safety data on an ad hoc basis for any immediate concerns that are observed. A separate unblinded team will handle any ad hoc production of unblinded tables, listings, and figures for ad hoc IDMC meetings. Blinded individuals will not be made aware of any unblinded data provided to the IDMC.

5.5.1 Breaking the Blind

The blind should not be broken. As needed to meet regulatory reporting requirements, designated pharmacovigilance personnel may be unblinded to treatment status of individual subjects. In this circumstance, and if there are no other concerns, neither BARDA nor the study staff (except the unblinded study staff member who prepares and administers the vaccine) will be unblinded to treatment status. In all cases where the blind is broken, the date, reason for code breaking, and the name and signature of the investigator who broke the blind will be recorded. Subjects whose study group assignment is unblinded will not receive any subsequent IP.

5.6 Treatment Compliance

The IP will be administered by an unblinded study staff member, and date, time, and location (left or right arm) of administration will be recorded in the subjects' eCRF. Subject compliance will be determined by the number and percentage of subjects who receive IP at each vaccination by study group. Any deviations from the dosing schedule outside the defined visit windows (Table 12–1 and Table 12–2) will be flagged in the clinical database.

5.7 Prior Vaccinations and Concomitant Medications

Use of all concomitant medications that the subject is taking at the time of Visit 1 (Day 1), medications taken up to 14 days prior to Visit 1 (Day 1), and vaccines received 12 months prior to Visit 1 (Day 1) will be recorded in the subject's eCRF. The minimum requirement is that drug name, dose, frequency, route of administration, and the dates of administration are to be recorded. This will include all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications. Any changes, additions, and/or deletions in concomitant medications and vaccinations also will be recorded in the subject's eCRF throughout the course of the subject's participation in the study.

Any concomitant medication deemed necessary for the welfare of the subject during the study may be given at the discretion of the investigator. However, it is the responsibility of the investigator to ensure that details regarding the medication are recorded in full in the eCRF.

Sites may contact the medical monitor regarding use of concomitant medications prior to enrollment for guidance as necessary. If it is discovered that a subject is using a prohibited concomitant medication after he or she is enrolled in the study, the site should contact the medical monitor to resolve the situation. All instances of use of prohibited concomitant medications must be documented in the eCRF. All vaccinations obtained outside of the study itself will be recorded while the subject is enrolled.

5.7.1 Prohibited Prior and Concomitant Medications

Immunosuppression as a result of an underlying illness or treatment or the use of anticancer chemotherapy or radiation therapy (cytotoxic) within the preceding 36 months prior to Day 1 (first vaccination) is prohibited. Long-term use (≥14 consecutive days) of glucocorticoids including oral or parenteral prednisone or equivalent (>20 mg total dose per day) or

high-dose inhaled steroids (>800 mcg/day of beclomethasone dipropionate or equivalent) within the preceding 1 month prior to screening is prohibited. Prior treatment with immunoglobulin or other blood product (with the exception of Rho[D] immune globulin) within 3 months prior to vaccination in this study is prohibited.

Receipt of any live vaccines within 4 weeks or inactivated vaccines within 2 weeks prior to Day 1 (first vaccination) until 21 days after the last vaccination is prohibited. This includes seasonal influenza vaccines. Receipt of an experimental agent (eg, vaccine, biologic, device, blood product, or medication) within 1 month prior to Day 1 (first vaccination) in this study or receipt of any experimental agent during the study period is prohibited.

5.7.2 Permitted Prior and Concomitant Medication

Low-dose (≤800 mcg/day of beclomethasone dipropionate or equivalent) inhaled and topical steroids are allowed.

Prohibited concomitant medication during the study may be given at the discretion of the investigator if deemed in the best interest of the subject's health. It is the responsibility of the investigator to ensure that details regarding the medication will be recorded in full in the eCRF.

6 Study Assessments and Procedures

Before performing any study-related procedures, the investigator will explain the study to potential subjects and all potential subjects will be given an ICF to read and sign. Subjects will have the opportunity to have any questions answered before signing the ICF. The investigator must address all questions raised by the subject. The investigator will also sign the ICF. The schedule of events is shown in Table 12–1 and Table 12–2.

6.1 Demographics and Medical History

Demographic data and a complete medical history (including prior and concomitant medical conditions/procedures, drug, alcohol, and tobacco use, as well as current use of herbal supplements and multivitamins) will be collected at screening and updated at Visit 1.

6.2 Safety Assessments

Safety assessments will include the following: vital sign measurements, physical examination, clinical safety laboratory tests, and solicited local and systemic reactogenicity symptoms, and occurrence of AEs, MAAEs, PIMMCs (see Appendix 2, Section 12.2), and SAEs. These assessments are detailed in Sections 6.2.1 through 6.2.5.

6.2.1 Vital Sign Measurements

Vital sign measurements will include oral temperature, pulse rate, and diastolic and systolic blood pressure (after subject is seated for at least 5 minutes).

6.2.2 Postvaccination Evaluation

At Visits 1 and 4 (Groups A-D, G-J) and at Visits 1, 4, and 8 (Groups E, F, K, L), subjects will be monitored for solicited (Section 6.2.5.2) and unsolicited AEs, SAEs, MAAEs, PIMMCs, and serious and suspected unexpected adverse reactions (SUSARs) for at least 30 minutes after vaccination. Details regarding collecting and reporting solicited local and systemic reactogenicity symptoms are presented in Section 6.2.5.2. Diary cards will be distributed according to Table 6–1 and will be used to record solicited local and systemic reactions. Solicited local and systemic reactogenicity will be toxicity graded.

After the subject has been monitored for 30 minutes after vaccination, the following evaluations will be performed:

1. Obtain 30±5-minute postvaccination vital sign measurements (oral temperature, pulse rate, and diastolic and systolic blood pressure) and toxicity grade.
2. Complete a 30±5-minute postvaccination injection site examination for solicited reactogenicity (local and systemic) and toxicity grade (see Section 6.2.5.2). If a visible injection-site abnormality is observed, document with a photograph[a].

[a] Photographs will be taken by study staff only in the event of abnormal findings (not expected with usual vaccine administration) for accurate description and evaluation of the findings and safety reviews. There are no digital format requirements; the photographs will not be stored in the study database and will not be used as part of the safety analysis. Photographs will be shared with the medical monitor, sponsor, and IDMC in a secure and blinded manner without exposing personal identification information (including tattoos). Subjects will be asked to provide informed consent requesting their permission to take a photograph of the finding for the purpose of medical management and safety evaluations.

6.2.3 Complete Physical Examination

A complete physical examination at screening will include the following: height (inches) and weight (pounds) and an assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, abdomen, lymph nodes, musculoskeletal system/extremities, and neurological system.

A targeted physical examination will be performed as mentioned in the schedule of events (Table 12–1 and Table 12–2) and at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities.

6.2.4 Clinical Safety Laboratory Tests

Clinical safety laboratory tests will include the following according to Table 12–1 and Table 12–2:

- hematology: complete blood count with differential and platelet count.
- coagulation: partial thromboplastin time and prothrombin time (international normalized ratio).
- chemistry/metabolic panel: ALT, AST, total bilirubin, creatinine, and blood urea nitrogen.

- urine pregnancy test: for female subjects of childbearing potential, a urine pregnancy test will be performed at screening, prior to vaccination on Days 1 and 22, and at any unscheduled visit (if clinically indicated) for all groups. In addition, the test will be performed prior to vaccination on Day 142 for Groups E, F, K, and L.

6.2.5 Adverse Events

6.2.5.1 Definitions of Adverse Events

The investigator is responsible for reporting all treatment-emergent AEs that are observed or reported during the study, regardless of their relationship to IP or their clinical significance.

An AE is defined as any untoward medical occurrence in a subject enrolled into this study regardless of its causal relationship to IP. Subjects will be instructed to contact the investigator at any time after randomization if any symptoms develop.

An SAE is defined as any event that results in any of the following:

- Death,
- Is immediately life threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, a blood dyscrasia or convulsion that does not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Medically attended AEs are defined as AEs with medically attended visits, including hospital, emergency room, urgent care clinic, or other visits to or from medical personnel (medical doctor, physician assistant, nurse practitioner) for any reason.

Potentially immune-mediated medical conditions are considered adverse events of special interest. The PIMMCs of concern for this study are detailed in Appendix 2, Section 12.2.

6.2.5.2 Solicited Local and Systemic Reactogenicity Symptoms

All subjects will record solicited local and systemic reactions and other unsolicited symptoms/complaints, including start and stop dates, on an 8-day diary card following each vaccination. The investigator or his/her designee will review the information from the diary card or from memory with the subject at each visit and grade reactogenicity using a standard toxicity grade (Appendix 3, Section 12.3). The diary card will be collected from the subjects and stored as a source document.

- Solicited local reactions at the injection site will include erythema/redness, induration/swelling, and pain.
- Solicited systemic reactions will include fever, myalgia, arthralgia, fatigue, headache, nausea, vomiting, diarrhea, and chills.

The above solicited local and systemic reactions will be recorded including start and stop dates, worst daily grade, any treatment required, and action taken. The investigator will assess if solicited local and systemic reactions will be considered as related to IP according to Section 6.2.5.6. The severity of local and systemic reactions will be graded using the FDA Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (Appendix 3, Section 12.3).

6.2.5.3 Assessing and Documenting Adverse Events

Adverse events will be assessed from the time the subject receives the first vaccination through Day 43 for Groups A-D and G-J and through Day 163 for Groups E, F, K, L. Medically attended adverse events, PIMMCs (Appendix 2, Section 12.2), and SAEs will be assessed from the time the subject receives the first vaccination until exit from the study. Additional details regarding eliciting and documenting local and systemic reactions are provided in Section 6.2.5.2.

At every study visit (except Visit 1), subjects will be asked a standard nonleading question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, received any vaccinations,

or changed concomitant medication regimens (both prescription and over-the-counter medications).

Subjects will be provided with diary cards to assist them in recording and reporting both unsolicited AEs and solicited local and systemic reactions (Section 6.2.5.2), according to Table 6–1.

Laboratory findings that qualify as AEs and nonqualifying laboratory abnormalities outside the laboratory's reference range will be toxicity graded according to the FDA Toxicity Grading Scale (Appendix 3, Section 12.3). Similarly, vital signs outside the clinic reference range will be graded according to the same scale. The toxicity grade for each identified laboratory finding and out-of-reference range vital sign will be documented in the study dataset.

The investigator will assess each Toxicity Scale Grade 1-4 finding and determine whether the finding is clinically significant. Grade 1-3 clinically significant findings will be categorized as AEs. An FDA toxicity Grade 2 (moderate) or greater (ie, ≥2.6 × ULN; see Appendix 3, Section 12.3) ALT and/or AST elevation (regardless of investigator-assessed clinical significance) will be entered into the AE reporting page. All Grade 4 findings (regardless of investigator-assessed clinical significance) will be graded as AEs. Other safety assessments (eg, vital sign measurements), or those identified from review of other documents (eg, diary card), including those that worsen from baseline, or are felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as AEs or SAEs.

For a laboratory finding assessed as an AE (see above), the investigator should report a medical condition rather than the name of the laboratory test abnormality whenever possible. For example, if the subject has a clinically significant Grade 1, 2, or 3 increased white blood cell count due to bronchitis, then the investigator should report the medical condition of "bronchitis" rather than "high white blood cell count." Similarly, a clinically significant decreased hemoglobin should be reported as "anemia" rather than "low hemoglobin," and a clinically significant decreased platelet count should be reported as "thrombocytopenia" rather than "low platelets."

Any clinically significant safety assessment that is associated with an underlying disease (unless explicitly identified above), unless judged by the investigator to be more severe than expected for the subject's condition, should not be reported as an AE.

Table 6–1 provides the safety data reporting periods used in this study.

Table 6–1 Schedule of Diary Cards and Safety Data Reporting Period

Diary Card Number	Type of Event	Vaccination Dose	Collection Period Days After Dosing (7 days After Each Vaccination)	Collection Period: Study Days	Study Groups
I	Solicited AEs Unsolicited AEs[a]	Dose 1	Postvaccination Days 1-8	Days 1-8	All
II	Unsolicited AEs[a]	Dose 1	Postvaccination Days 9-21	Days 9-21	All
III	Solicited AEs Unsolicited AEs[a]	Dose 2	Postvaccination Days 1-8	Days 22-29	All
IV	Unsolicited AEs[a]	Dose 2	Postvaccination Days 9-21	Days 30-43	All
V	Solicited AEs Unsolicited AEs[a]	Dose 3	Postvaccination Days 1-8	Days 142-149	Groups E, F, K, L
VI	Unsolicited AEs[a]	Dose 3	Postvaccination Days 9-21	Days 150-163	Groups E, F, K, L
NA	SAEs, MAAEs, and PIMMCs		Entire study period[b]		All
NA	Pregnancies		Entire study period[c]		All

Abbreviations: AE, adverse event; MAAE, medically attended adverse event; PIMMC, potentially immune-mediated medical condition; SAE, serious adverse event.

[a] Unsolicited AEs will be collected through the end of the study visit window for each AE collection period (ie, 21 days after each vaccination ±3-day window = 21 ±3 days).

[b] The entire study period is from the time a subject receives the first study injection through the end-of-study visit. If the investigator becomes aware of any related SAE or related MAAE after exit from or completion of the study, he or she is obligated to report this event.

[c] Pregnancies that occur during a subject's participation in the study will be followed until resolution and 2 weeks after live birth even if the pregnancy ends after the end-of-study visit.

6.2.5.4 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page in the eCRF. Information to be collected includes event term, time of onset, investigator-specified assessment of severity and relationship to IP, time of resolution of the event, seriousness, any required treatment or evaluations, and outcome. Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses (unless judged by the investigator to be expected for the subject's underlying condition), reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed to adequate resolution or stabilization. The latest version of the Medical Dictionary for Regulatory Activities

(MedDRA) at the time of study startup will be used to code all AEs. Additional details regarding reporting of local and systemic reactions are provided in Section 6.2.5.2.

Any medical condition that is present at the time that the subject is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates beyond what is expected for that condition at any time during the study, it should be recorded as an AE.

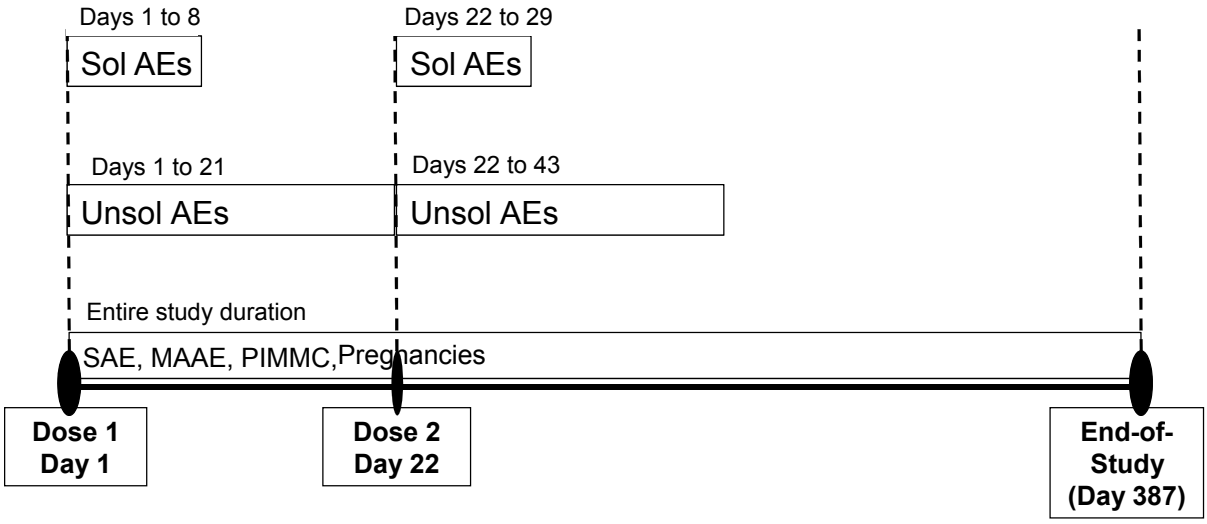
Any AE that meets SAE or PIMMC criteria (Section 6.2.5.1 and Appendix 2, Section 12.2) must be reported to PPD immediately (ie, within 24 hours) after the time site personnel first learn about the event. The following contact information is to be used for SAE reporting:

SAE Hotline: [redacted]

SAE Fax line: [redacted]

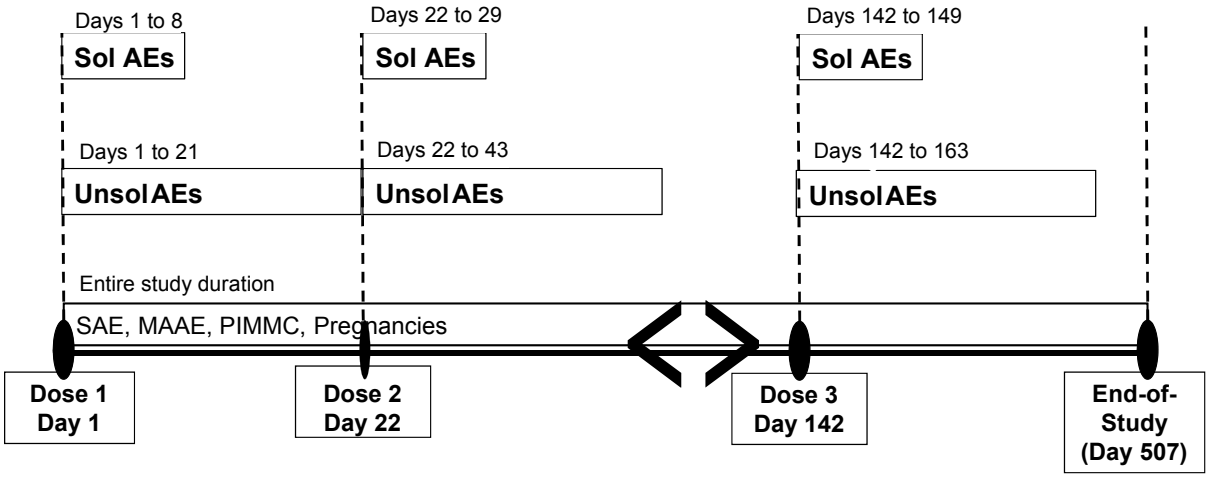
The safety event reporting periods are shown in Figure 6-1 for Groups A to D and G to J and Figure 6-2 for Groups E, F, K, and L. Solicited AEs will be collected for 7 days after each vaccination. Unsolicited AEs will be collected for 21 days after each of 2 vaccine doses (Groups A-D and G-J) and for 21 days after each of 3 vaccine doses (Groups E, F, K, and L). Serious adverse events and PIMMCs will be collected for approximately 13 months after the first study vaccine dose (Groups A-D and G-J) and for approximately 17 months after the first study vaccine dose (Groups E, F, K, and L).

Figure 6-1 Safety Event Reporting Period, Groups A to D, G to J



Abbreviations: AE, adverse event; MAAE, medically attended adverse event; PIMMC, potentially immune-mediated medical condition; SAE, serious adverse event; Sol, solicited; Unsol, unsolicited.

Figure 6-2 Safety Event Reporting Period, Groups E, F, K, L



Abbreviations: AE, adverse event; MAAE, medically attended adverse event; PIMMC, potentially immune-mediated medical condition; SAE, serious adverse event; Sol, solicited; Unsol, unsolicited.

6.2.5.5 Assessment of Severity

The severity of an AE refers to the extent to which an AE affects the subject's daily activities. All solicited AEs will be graded according to the FDA Toxicity Grading Scale (Appendix 3, Section 12.3) and entered into the AE reporting page. Grade 1-3 hematology or serum chemistry values determined by the investigator to be clinically significant will be entered into the AE reporting page. An FDA toxicity Grade 2 (moderate) or greater (ie, ≥2.6 × ULN; see Appendix 3, Section 12.3) ALT and/or AST elevation (regardless of investigator-assessed clinical significance) will be entered into the AE reporting page, and the grading will be consistent with the FDA toxicity score. All Grade 4 laboratory findings are considered AEs regardless of the investigator's determination of clinical significance and should also be entered using the FDA toxicity score for severity. In all other cases, the severity of each AE will be rated as mild, moderate, or severe using the following criteria:

Mild:	An event usually transient in nature and generally not interfering with normal activities.
Moderate:	An AE that is sufficiently discomforting to interfere with normal activities.
Severe:	An AE that is incapacitating and/or prevents normal activities.

Changes in the intensity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode. The severity of solicited AEs will be classified.

6.2.5.6 Assessment of Causality

The investigator's assessment of the relationship between an AE and study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of the IP in causing or contributing to the AE will be characterized using the following classification and criteria:

Unrelated: This relationship suggests that there is not a reasonable possibility[a] that the AE is related to the IP.

Related: This relationship suggests that there is a reasonable possibility[a] that the AE is related to the IP.

Note: The investigator should consider the package inserts of all products administered in this study when determining causality.

[a] Reasonable possibility means there is evidence to suggest a causal relationship between the IP and the AE.

6.2.5.7 Assessing Expectedness

Expected AEs are AEs consistent with the applicable product information provided by the sponsor (the investigator brochures for IP). The sponsor, in consultation with the medical monitor, determines expectedness of SAEs and MAAEs. The sponsor and medical monitor should consider the package inserts of all products administered in this study when determining expectedness. If the assessment is that the SAE or MAAE is expected, no further reporting is required. If the medical monitor's assessment is that the SAE or MAAE is unexpected, then the event may represent a SUSAR or expedited SAE for reporting purposes.

6.2.5.8 Follow-Up of Subjects Reporting Adverse Events

All AEs must be reported in detail on the appropriate page in the eCRF and followed to satisfactory resolution, until the investigator deems the event to be chronic or not clinically significant, or until the subject is considered to be stable. In the case of an abnormal laboratory value that is entered as an AE due to toxicity grade parameters (ie, clinically significant Grade 1 to 3, Grade 4 [regardless of clinical significance], and ALT and/or AST elevations ≥2.6 × ULN), the subject will be required to have a repeat laboratory test with results assessed by the investigator and continued monitoring until the results return to the screening baseline value (ie, baseline toxicity score) or are considered stable with a new baseline. Subjects may not receive revaccination if ALT and/or AST elevations reach ≥2 by FDA toxicity score and do not return to the screening baseline value (ie, baseline toxicity score) by the time of revaccination.

6.3 Immunogenicity Assessments

Immunogenicity assessments will include the following assessments at Day 1, Day 22, Day 43, and Day 142 (Groups A-D, G-J) and at Day 1, Day 22, Day 43, Day 142, Day 163, and Day 262 (Groups E, F, K, L).

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

The details on the handling, processing, and shipping will be provided in the Laboratory Manual.

6.4 Pregnancy

Pregnancy is not regarded as an AE unless there is a suspicion that an IP may have interfered with the effectiveness of a contraceptive medication. Any pregnancy that occurs during study participation must be reported using a clinical study pregnancy form. If a subject becomes pregnant, she will not have any invasive procedures performed and will not receive any further vaccinations, as normally mandated by the protocol. The subject will undergo all other evaluations according to the schedule of events (Table 12–1 and Table 12–2). To ensure subject safety, each pregnancy must be reported to the sponsor, BARDA, within 2 weeks of learning of its occurrence. The pregnancy must be followed up to resolution and 2 weeks after live birth to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the subject was discontinued from the study or if the pregnancy ends after the end-of-study visit (Visit 9 [Groups A-D, G-J] and Visit 14 [Groups E, F, K, L]). Pregnancy complications

and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous miscarriages must be reported as an SAE.

6.5 Sample Collections

Procedures for the handling and processing of biological samples are provided in the Laboratory Manual.

The hematology, coagulation, and chemistry/metabolic panel laboratory analyses will be performed at a central laboratory. Reference ranges will be used by the investigator to assess the laboratory data for clinical significance and pathological changes and will be graded according to the FDA Toxicity Grading Scale (Appendix 3, Section 12.3).

The samples collected for immunogenicity testing and cell-mediated assays will be stored in appropriate conditions as specified in the Laboratory Manual until shipped for testing at a facility designated by the sponsor.

7 Statistical and Analytical Plan

This is a descriptive study and no formal hypotheses for the primary endpoints are being tested. The main purpose of this study is to assess the ability of H5 influenza vaccines and adjuvants present in the NPIVS to generate an immune response to homologous and to antigenically distant heterologous H5 influenza virus strains. The primary outcomes will be descriptive in terms of whether the study vaccines are safe and immunogenic.

7.1 Primary Endpoints

- Safety: Occurrence of mild, moderate, or severe solicited local and systemic reactogenicity symptoms during the 8 days postvaccination, inclusive of the vaccination day
- Immunogenicity: SPR (defined as the proportion of subjects achieving a serum HAI titer of at least 1:40 against influenza antigen) against strains contained in the vaccines on Day 43 for Groups A-D and G-J and on Day 163 for Groups E, F, K, L

7.2 Secondary Endpoints

Secondary Safety Endpoints:

- Occurrence of SAEs, MAAEs, and PIMMCs in 12 treatment groups through 12 months after the last dose of study vaccine
- Occurrence of any AEs leading to study withdrawal
- Frequency and severity of unsolicited AEs for 21 days following each vaccination
- Occurrence of clinical safety laboratory abnormalities at all collected time points
- Occurrence of vital sign abnormalities at all collected time points

Secondary Immunogenicity Endpoints:

- Serum HAI and MN antibody responses at all collected time points
- SPR of serum HAI antibody at collected time points

- Seroconversion rate (defined as proportion of subjects achieving either a prevaccination antibody titer of <1:10 and a postvaccination titer of at least 1:40 or a prevaccination antibody titer of at least 1:10 and a 4-fold or greater increase of postvaccination antibody titer; if antibody titer is undetectable, it will be assigned a value of half the lower limit of detection) at all collected postvaccination time points

7.3 Exploratory Endpoints

Exploratory Immunogenicity Endpoints:

- Peripheral antibody responses to epitopes within the influenza virus surface proteins HA or neuraminidase at all collected time points
- Cell-mediated (eg, B cell, CD4+ T cell, CD8+ T cell) responses in a subset composed of approximately half of enrolled subjects using PBMCs at all collected time points

7.4 Sample Size Calculations

Approximately 720 subjects with 60 subjects per study group will be enrolled in the study. Approximately half of enrolled subjects will be selected to provide a blood sample for PBMC collection.

The number of subjects proposed to be enrolled in this protocol is based upon previous experience with similar studies such as the Mix and Match Studies (NCT 01317745 and NCT 01217758) performed by Division of Microbiology and Infectious Diseases/National Institute of Allergy and Infectious Diseases. These prior studies had study groups of similar size that proved to be sufficient to allow the collection of meaningful data, especially with respect to acute solicited AEs and antibody results. While the current study is not designed to test specific hypotheses, Table 7–1 and Table 7–2 indicate the power of the proposed sample size to detect a range of common, immediate postvaccination elicited safety events as well as to meet the success criteria for SPR.

Table 7–1 Safety – Power for Detecting at Least 1 SAE, MAAE, or a Grade 3 Solicited AE

True Event Rate (%)	Power (%) N = 60	Power (%) N = 120
0.1	5.8	11.3
0.5	26.0	45.2
1	45.3	70.1
2	70.2	91.2
3	83.9	97.4
4	91.4	99.3
5	95.4	99.8

Abbreviations: AE, adverse event; MAAE, medically attended adverse event; SAE, serious adverse event.
Note: The exact method was used for the calculations in this table.
Note: Serious adverse events and MAAEs will be collected for approximately 12 months after the last study vaccine dose.
Note: Solicited AEs will be collected for 7 days after each of the vaccine doses.

Table 7–2 Immunogenicity – Power for Meeting Success Criteria of SPR

Success Criteria (%)	Proportion of Subjects Achieving a Serum HAI Antibody Titer of at Least 1:40 for the Testing Vaccine (%)	Power (%) N = 60	Power (%) N = 120
70	90	98.5	>99.9
	85	81.9	99.0
	80	44.9	79.0

Abbreviations: HAI, hemagglutination inhibition; SPR, seroprotection rate.

7.5 Analysis Sets

The following analysis sets will be used in the statistical analyses.

Full analysis set (FAS): The FAS will consist of all subjects who are randomly assigned to receive IP. All analyses using the FAS will group subjects according to randomized treatment.

Safety set: The safety set will consist of all subjects who are randomly assigned and receive at least 1 dose of IP. Safety endpoint summaries and listings will be performed on the safety set using study group treatment actually received.

Immunogenicity-full analysis set (IFAS): The IFAS will consist of all subjects who are randomly assigned, receive at least 1 dose of IP, and have at least 1 valid postvaccination and

determinate assay result. As supportive analysis, all the immunogenicity endpoint summaries will be performed on the IFAS by actual treatments received.

Immunogenicity per-protocol set (IPPS): The IPPS is a subset of the IFAS, where all subjects meet the IFAS criteria and must meet the following criteria:

- have received all the doses of IP to which they were randomly assigned
- have valid and determinate assay result for HAI at Day 43 for Groups A-D and G-J, and Day 163 for Groups E, F, K, L
- have no significant protocol deviations that are determined to potentially interfere with the immunogenicity assessment of IP.

All the immunogenicity endpoint summaries will be performed primarily on the IPPS using treatment actually received.

7.6 Description of Subgroups to be Analyzed

No subgroup analyses are planned.

7.7 Statistical Analysis Methodology

Study data will be summarized with descriptive statistics (mean, standard deviation, median, minimum, maximum, and number of observations) for quantitative parameters and by incidence rates and the corresponding 95% confidence intervals (CIs) for categorical findings as appropriate.

No formal significance testing will be performed. Details of the statistical analyses, methods, and data conventions are described in the statistical analysis plan.

7.7.1 Subject Disposition

Subject disposition will be summarized by study group and will include subjects who are enrolled, randomly assigned, discontinue, and complete the study. For discontinued subjects, reasons for discontinuation will be summarized.

7.7.2 Analyses of Demographic and Baseline Characteristics

Demographic and baseline characteristics, such as age, gender, race, body weight, height, and medical history will be summarized by study group using descriptive statistics.

7.7.3 Analysis of Primary Endpoints

7.7.3.1 Analysis of Primary Safety Endpoint

Solicited local and systemic reactions (recorded as AEs, Section 6.2.5.2) during the 8 days after each vaccination, inclusive of the vaccination day, will be summarized as a frequency table that includes 95% exact CIs by study group and by the degree of severity (mild, moderate, or severe).

7.7.3.2 Analysis of Primary Immunogenicity Endpoint

The SPR and corresponding 95% CIs of HAI antibody responses against strains contained in the vaccine at Day 43 for Groups A-D and G-J, and Day 163 for Groups E, F, K, L will be summarized for each study group.

7.7.4 Analysis of Secondary Endpoint

7.7.4.1 Analysis of Secondary Safety Endpoint

Serious adverse events, MAAEs, PIMMCs, and AEs leading to study withdrawal will be summarized by study group and system organ class (SOC)/preferred term (PT).

Unsolicited AEs (including clinically significant laboratory and vital sign abnormalities) for 21 days following each vaccination will be summarized by study group, SOC/PT, and further summarized by severity and relatedness.

Clinical safety laboratory abnormalities will be summarized at prevaccination and 7 days after each vaccination by study group.

7.7.4.2 Analysis of Secondary Immunogenicity Endpoint

Geometric mean titers and the corresponding 95% CIs of serum HAI and MN antibody responses will be summarized at all collected time points.

The SPR and corresponding 95% CIs for HAI antibodies will be summarized by study group at all collected time points.

The SCR and the corresponding 95% CIs for both HAI and MN antibodies will be summarized by study group at all collected postvaccination time points.

7.7.5 Analyses of Exploratory Immunogenicity Endpoint

The exploratory analyses will be described in the statistical analysis plan.

7.7.6 Other Analyses

Prior and posttreatment physical examination findings, the number and percentage of subjects who receive 1, 2, and 3 total doses of IP will be summarized by study group.

7.7.7 Interim Analyses

Interim analyses will be performed based on cumulative immunogenicity and safety data at Day 43 and Day 163 for all study groups. At each time point the study database will be monitored, cleaned, and frozen through the data cut time point. The study team, except the unblinded team members, should remain blind until final database lock and unblinding. Interim analysis results will be unblinded at the group level, and each group will be assigned a fake name. Results will be provided to the sponsor with groups identified only by their fake names.

7.8 Data Quality Assurance

The sponsor will perform quality control and assurance checks on all clinical studies that it sponsors. Before enrolling any subjects in this study, sponsor personnel and the investigator will review the protocol, the package inserts, investigator brochures, the eCRFs and instructions for their completion, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs. A qualified representative of the sponsor will monitor the conduct of the study by visiting the site and by contacting the site by telephone and e-mail. During these site visits, information recorded in the eCRFs will be verified against source documents.

7.8.1 Data Management

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include laboratory reports.

Study site staff will enter subject data into Medidata RAVE. The analysis data populations will be a combination of these data and data from other sources (eg, laboratory data).

Clinical data management will be performed in accordance with applicable PPD and/or BARDA standards and data cleaning procedures to ensure the integrity of the data, eg, removing errors and inconsistencies in the data. Adverse events (including SAEs, MAAEs, and PIMMCs) and concomitant medication terms will be coded using the MedDRA and WHODrug dictionaries, respectively.

After database lock, each site will receive a Compact Disc Read-Only Memory (CDROM) containing all of their site-specific eCRF data as entered into Medidata RAVE for the study, including full discrepancy and audit history. Additionally, a CDROM copy of all of the site's data from the study will be created and sent to the sponsor for storage. PPD will maintain a duplicate CDROM copy for their records. In all cases, subject names or initials will not be collected by or transmitted to the sponsor.

8 Ethics

8.1 Institutional Review Board

Federal regulations and the International Council for Harmonisation (ICH) guidelines require that approval be obtained from an institutional review board (IRB) before participation of human subjects in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study to be provided to the subject or the subject's legal guardian must be approved by the IRB. Documentation of all IRB approvals and of the IRB compliance with ICH harmonised tripartite guideline E6(R1): Good Clinical Practice (GCP) will be maintained by the site and will be available for review by the sponsor or its designee.

All IRB approvals should be signed by the IRB chairman or designee and must identify the IRB name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB. The investigator must promptly supply the sponsor or its designee, the IRB, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to subjects.

8.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, and all applicable regulations.

8.3 Subject Information and Consent

A written informed consent in compliance with regulatory authority regulations and US Title 21 Code of Federal Regulations (CFR) Part 50 shall be obtained from each subject before entering the study or performing any unusual or nonroutine procedure that involves risk to the subject. An informed consent template may be provided by the sponsor to sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the sponsor or its designee or both before IRB submission. Once reviewed, the consent will be submitted by the investigator to his or her

IRB for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating subjects must sign the revised form.

Before recruitment and enrollment, each prospective subject or his or her legal guardian will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured that the subject/legal guardian understands the implications of participating in the study, the subject/legal guardian will be asked to give consent to participate in the study by signing the ICF.

Using the ICF, subjects who participate in this study will also be asked 3 questions (included in Section 3.1.4). The investigator shall retain the signed original ICF(s) and give a copy of the signed original form to the subject or legal guardian.

9 Investigator's Obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB but will not result in protocol amendments.

9.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject (or the subject's legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, the FDA, or the IRB.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

9.2 Financial Disclosure

Investigators and subinvestigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigators and subinvestigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

9.3 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R1) 8.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to:

- IRB approval
- Original investigator-signed investigator agreement page of the protocol

- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572
- Current (within 2 years) curriculum vitae for the investigator and each subinvestigator listed on Form FDA 1572
- Medical licenses for all investigators
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigators and subinvestigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- Executed clinical study agreement
- Documentation of Federal Wide Assurance number and expiration date
- IRB-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the subject or legal guardian
- Site delegation log
- Documentation of human subjects protection training by all staff listed on the site delegation log
- Laboratory certifications and normal ranges for central laboratory, in accordance with 42 CFR 493
- Centers for Laboratory Improvement Amendments Waiver for pregnancy tests performed onsite

9.4 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6(R1) and 21 CFR 312. The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical study registers before enrollment of subjects begins.

9.5 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R1) and 21 CFR 312 and all applicable guidelines and regulations.

9.6 Adverse Events and Study Report Requirements

By participating in this study, the investigator agrees to submit reports of SAEs according to the time line and method outlined in the protocol. In addition, the investigator agrees to submit annual reports to the site IRB as appropriate.

9.7 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB with a summary of the study's outcome and the sponsor and regulatory authority(ies) with any reports required.

9.8 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP, as described in 21 CFR 312.62. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

9.9 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and will determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The sponsor has final approval authority over all such issues.

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

10 Study Management

10.1 Monitoring

All aspects of the study will be carefully monitored, by the sponsor or its designee, for compliance with applicable government regulation with respect to current GCP and current standard operating procedures. Investigational product accountability will be monitored by a separate unblinded monitor.

10.1.1 Safety Monitoring: Responsibilities for Ensuring the Safety of Study Subjects

The regulatory authority, BARDA, the institution where the research is performed, and all members of the investigator's clinical team share responsibility for ensuring that participants in this study are exposed to the least possible risk of AEs that may result from participation in this protocol.

10.1.2 Principal Investigator

The principal investigator has a personal responsibility to closely monitor study subjects and an inherent authority to take whatever measures necessary to ensure their safety. The principal investigator has the authority to terminate, suspend, or require changes to a clinical study for safety concerns and may delay an individual's study IP administration if the principal investigator has some suspicion that the study vaccine might place a subject at significant risk. Where specified, responsibilities of the principal investigator may be delegated to a medically qualified team member (designee). The principal investigator or designee determines severity and causality with respect to the study IP for each AE.

10.1.3 Study Sponsor

The sponsor also has an institutional responsibility to ensure subject safety. This responsibility is vested in a medical monitor and an IDMC.

10.1.4 Medical Monitor

The medical monitor is the sponsor's representative and is a physician or surgeon in the United States. The medical monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, monitor for study

pausing rules, and discuss the conduct of the study with the investigator and personnel. The medical monitor reviews the safety of the IP for protocols in a specific region and, in conjunction with the sponsor, determines expectedness of the AE. The medical monitor, in consultation with the sponsor, will review causality for SAEs/MAAEs/PIMMCs and may discuss the causality with the investigator or designee. The medical monitor, like the investigator, will be blinded for the subjects' study group assignments.

10.1.5 Independent Data Monitoring Committee

The IDMC will operate according to the IDMC Charter. The IDMC will review study progress and oversee clinical, safety, and reactogenicity data on an ad hoc basis; the IDMC will meet only if a pausing rule is met. The IDMC will be composed of 3 members with expertise in the conduct and safety oversight of vaccine clinical studies. One of the IDMC members will serve as the IDMC chairperson.

The IDMC may recommend suspension or resumption of enrollment and study vaccine administration after review of safety data. However, the sponsor will make the final decision to suspend or resume study activities. The recommendations of the IDMC, along with the sponsor's decision, will be communicated to the investigators, the IRB, and regulatory agency.

10.1.6 Institutional Review Board

The IRB has institutional responsibility for the safety of study subjects. The IRB has the authority to terminate, suspend, or require changes to a clinical study. The sponsor or its designee agrees to abide by any directives issued by the IRB.

10.1.7 Regulatory Authority

As this study is conducted under a US Investigational New Drug Application, the FDA has the authority to place the study on a regulatory clinical hold for modification, suspension, or termination of the study. The sponsor or its designee agrees to abide by any directives issued by the regulatory agency.

10.1.8 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to all study records.

In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor, or a regulatory agency (eg, FDA) access to all study records.

The investigator should promptly notify the sponsor and PPD of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

10.2 Management of Protocol Amendments and Deviations

10.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the subject, must be reviewed and approved by the sponsor or its designee. Full amendments to the protocol must be approved by the IRB before subjects can be enrolled into an amended protocol. Letters of amendment or clarification do not need to be approved by the IRB.

10.2.2 Protocol Deviations

The investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study subjects without prior IRB approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol by the subject or investigator that results in a significant, additional risk to the subject or that may affect the study outcome. Significant deviations can include nonadherence to inclusion or exclusion criteria or nonadherence to FDA regulations or ICH GCP guidelines, and may lead to the subject being withdrawn from the study (ie, no longer receive IP, see Section 4.2).

Neither the sponsor nor designee will authorize deviations to the study. Deviations from the protocol are not permitted except to protect the safety of a subject.

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Investigators will be notified in writing by the monitor of deviations. The IRB should be notified of all significant protocol deviations in a timely manner, as defined by the IRB.

10.3 Study Termination

Although BARDA has every intention of completing the study, BARDA reserves the right to discontinue the study at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last subject completes Visit 9 (end-of-study visit) for Groups A-D and G-J (Table 12–1) and Visit 14 (end-of-study visit) for Groups E, F, K, and L (Table 12–2).

10.4 Final Report

Whether the study is completed or prematurely terminated, the sponsor will ensure that the CSRs are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor will also ensure that the CSRs in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of CSRs.

A final CSR will be written with unblinded data at the subject level through Day 142 for Groups A-D and G-J and through Day 262 for Groups E, F, K, and L. Additional long-term safety results will be included in an addendum to the final CSR.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the CSR. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the CSR, the sponsor will provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate. The study results will be posted on publicly available clinical study registers.

11 Reference List

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12 Appendices

12.1 Appendix 1: Schedule of Events

Table 12–1 Schedule of Events, Groups A to D, G to J

Study visit	Screening	V1	V2[a]	V3	V4	V5[a]	V6	V7	V8	V9[a] (EOS)	ET	Unsch
Study day	**-14 to -3**	**1**	**4**	**8**	**22**	**25**	**29**	**43**	**142**	**387**	**N/A**	**N/A**
Window allowance (days)			**V1+3 (±1)**	**V1+7 (±1)**	**V1+21 (+3)**	**V4+3 (±1)**	**V4+7 (±1)**	**V4+21 (±3)**	**V1+141 (±7)**	**V1+386 (±7)**	**N/A**	**N/A**
Obtain informed consent	X[b]											
Vital sign measurements[c]	X	X		X	X		X	X			X	X[d]
Height and weight	X	X[e]										
Medical history	X	X[e]										
Perform subject interview[f]			X	X	X	X	X	X	X	X	X	X
Review diary card[g]			X	X	X	X	X	X			X[h]	X[h]
Distribute diary card[g] and review instructions		X DCI		X DCII	X DCIII		X DCIV					
Distribute measuring tool and thermometer and review instructions		X			X							
Collect diary card[g]				X DCI	X DCII		X DCIII	X DCIV				
Concomitant medications	X[i]	X[e,i]	X	X[j]	X[e]	X	X[j]	X	X	X	X	X
Concomitant vaccinations	X[i]	X[e,i]	X	X[j]	X[e]	X	X[j]	X	X	X	X	X
Complete physical examination[k]	X											
Targeted physical examination[l]		X[e]		X	X[e]		X				X[d]	X[d]
Urine pregnancy test (WOCBP)	X	X[e,m]			X[e,m]							X[d]
Review inclusion and exclusion criteria	X	X[e]			X[e]							

Table 12–1 Schedule of Events, Groups A to D, G to J

Study visit	Screening	V1	V2[a]	V3	V4	V5[a]	V6	V7	V8	V9[a] (EOS)	ET	Unsch
Study day	**-14 to -3**	**1**	**4**	**8**	**22**	**25**	**29**	**43**	**142**	**387**	**N/A**	**N/A**
Window allowance (days)			**V1+3 (±1)**	**V1+7 (±1)**	**V1+21 (+3)**	**V4+3 (±1)**	**V4+7 (±1)**	**V4+21 (±3)**	**V1+141 (±7)**	**V1+386 (±7)**	**N/A**	**N/A**
Venous blood sample collection for clinical safety laboratory tests[n]	X			X[o]	X[e,o]		X[o]					X[d]
Venous blood sample collection for antibody assays		X[e]			X[e]			X	X			
Cellular immunology (subset only)		X[e]			X[e]			X	X			
Randomization		X[e]										
Vaccination		X			X[p]							
Monitor subject for 30 minutes following vaccination[q]		X			X							
Examine vaccination site[r]		X[s]		X	X[s]		X				X[d]	X[t]
AE/MAAE/PIMMC/SAE assessment[u]		X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DC, diary card; eCRF, electronic case report form; EOS, end of study; ET, early termination; FDA, Food and Drug Administration; MAAE, medically attended adverse event; N/A, not applicable; PIMMC, potentially immune-mediated medical condition; SAE, serious adverse event; SUSAR, suspected unexpected serious adverse reaction; ULN, upper limit of normal; Unsch, unscheduled; V, visit; WOCBP, women of childbearing potential.

[a] Telephone call assessment.

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

[c] Vital sign measurements include oral temperature, pulse rate, and blood pressure. Vital signs will be measured before blood is collected, at both pre-vaccination and 30±5-minute postvaccination time points on a vaccination day. Diastolic and systolic blood pressure will be measured after the subject is seated for at least 5 minutes.

[d] If clinically indicated.

[e] Prior to vaccination.

[f] Ask subject a standard nonleading question to elicit any medically related changes in their well-being. Ask if they have been hospitalized, had any accidents, used any new medications, received any vaccinations, or changed concomitant medication regimens (both prescription and over-the-counter medications).

[g] Diary Card I (Days 1-8) and III (Days 22-29) will be used to collect unsolicited and solicited local and systemic reactions. Diary Card II (Days 9-21) and IV (Days 30-43) will be used to collect unsolicited AEs.

[h] If applicable, according to the protocol period, collect and review DC with subject.

[i] Use of all concomitant medications that the subject is taking at the time of Visit 1, medications taken up to 14 days prior to Visit 1, and vaccines received 12 months prior to Visit 1 will be recorded in the subject's eCRF.

[j] Obtained by interview and by review of diary card completed by the subject.

[k] Any physical examination findings will be collected in the eCRF for medical history data presentation.

[l] Targeted physical examination will be performed at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities. Any findings from this examination will be collected in the eCRF for AEs.

[m] A urine pregnancy test must be performed within 24 hours prior to vaccination and pregnancy test results must be final and negative prior to vaccination.

[n] Hematology: complete blood count with differential, platelet count; coagulation: partial thromboplastin time and prothrombin time (international normalized ratio); chemistry/metabolic panel: ALT, AST, total bilirubin, creatinine, and blood urea nitrogen.

[o] For abnormal laboratory results that are clinically significant and for ALT and/or AST elevations ≥2.6 × ULN, repeat test until resolved or results become stable (see Section 6.2.5.8).

[p] Subjects with an acute illness, including body temperature greater than 100.4°F, immediately prior to each vaccination or, per subject report, within 3 days prior to a scheduled vaccination in this study can be rescheduled for vaccination as long as the vaccination visit is within the visit window. Subjects with a Grade ≥3 AE that has not returned to baseline or stabilized will not be revaccinated. Subjects with a serum ALT and/or AST elevation that is Grade 2 (moderate) or greater based on FDA toxicity grading (ie, ≥2.6 × ULN) will not be revaccinated unless the value resolves on repeat testing to the screening baseline value (ie, baseline toxicity score) and the subject remains within the visit window allowance (see Section 4.3).

[q] At Visits 1 and 4, subjects will be monitored for solicited and unsolicited AEs, SAEs, MAAEs, PIMMCs, and SUSARs for at least 30 minutes after vaccination; concomitant medications will be recorded.

[r] Examine vaccination site for erythema/redness and swelling and monitor for pain.

[s] At Visits 1 and 4, complete a 30±5-minute postvaccination injection site examination for erythema/redness and swelling and monitor for pain. If a visible injection-site abnormality is observed, document with a photograph.

[t] If the unscheduled visit occurs within 7 days after either of the 2 study vaccinations.

[u] Only MAAEs, PIMMCs (see Appendix 2, Section 12.2), and SAEs will be collected after Day 43, all other AEs will be collected through 21 days following each vaccination.

Table 12–2 Schedule of Events, Groups E, F, K, L

Study visit	Screening	V1	V2[a]	V3	V4	V5[a]	V6	V7	V8	V9[a]	V10	V11	V12	V13[a]	V14[a] (EOS)	ET	Unsch
Study day	**-14 to -3**	**1**	**4**	**8**	**22**	**25**	**29**	**43**	**142**	**145**	**149**	**163**	**262**	**322**	**507**	**N/A**	**N/A**
Window allowance (days)			**V1+3 (±1)**	**V1+7 (±1)**	**V1+21 (+3)**	**V4+3 (±1)**	**V4+7 (±1)**	**V4+21 (±3)**	**V1+141 (±7)**	**V8+3 (±1)**	**V8+7 (±1)**	**V8+21 (±3)**	**V1+261 (±7)**	**V1+321 (±7)**	**V1+506 (±7)**	**N/A**	**N/A**
Obtain informed consent	X[b]																
Vital sign measurements[c]	X	X		X	X		X	X	X		X	X	X			X	X[d]
Height and weight	X	X[e]															
Medical history	X	X[e]															
Perform subject interview[f]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review diary card[g]			X	X	X	X	X	X		X	X	X				X[h]	X[h]
Distribute diary card[g] and review instructions		X DCI		X DCII	X DCIII		X DCIV		X DCV		X DCVI						
Distribute measuring tool and thermometer and review instructions		X			X				X								
Collect diary card[g]				X DCI	X DCII		X DCIII	X DCIV			X DCV	X DCVI					

Table 12–2 Schedule of Events, Groups E, F, K, L

Study visit	Screening	V1	V2[a]	V3	V4	V5[a]	V6	V7	V8	V9[a]	V10	V11	V12	V13[a]	V14[a] (EOS)	ET	Unsch
Study day	**-14 to -3**	**1**	**4**	**8**	**22**	**25**	**29**	**43**	**142**	**145**	**149**	**163**	**262**	**322**	**507**	**N/A**	**N/A**
Window allowance (days)			**V1+3 (±1)**	**V1+7 (±1)**	**V1+21 (+3)**	**V4+3 (±1)**	**V4+7 (±1)**	**V4+21 (±3)**	**V1+141 (±7)**	**V8+3 (±1)**	**V8+7 (±1)**	**V8+21 (±3)**	**V1+261 (±7)**	**V1+321 (±7)**	**V1+506 (±7)**	**N/A**	**N/A**
Concomitant medications	X[i]	X[e,i]	X	X[j]	X[e]	X	X[j]	X	X[e]	X	X[j]	X	X	X	X	X	X
Concomitant vaccinations	X[i]	X[e,i]	X	X[j]	X[e]	X	X[j]	X	X[e]	X	X[j]	X	X	X	X	X	X
Complete physical examination[k]	X																
Targeted physical examination[l]		X[e]		X	X[e]		X		X[e]		X					X[d]	X[d]
Urine pregnancy test (WOCBP)	X	X[e,m]			X[e,m]				X[e,m]								X[d]
Review inclusion and exclusion criteria	X	X[e]			X[e]				X[e]								
Venous blood sample collection for clinical safety laboratory tests[n,o]	X			X	X		X		X		X						X[d]
Venous blood sample collection for antibody assays		X[e]			X[e]			X	X[e]			X	X				
Cellular immunology (subset only)		X[e]			X[e]			X	X[e]			X	X				

Table 12–2 Schedule of Events, Groups E, F, K, L

Study visit	Screening	V1	V2[a]	V3	V4	V5[a]	V6	V7	V8	V9[a]	V10	V11	V12	V13[a]	V14[a] (EOS)	ET	Unsch
Study day	**-14 to -3**	**1**	**4**	**8**	**22**	**25**	**29**	**43**	**142**	**145**	**149**	**163**	**262**	**322**	**507**	**N/A**	**N/A**
Window allowance (days)			**V1+3 (±1)**	**V1+7 (±1)**	**V1+21 (+3)**	**V4+3 (±1)**	**V4+7 (±1)**	**V4+21 (±3)**	**V1+141 (±7)**	**V8+3 (±1)**	**V8+7 (±1)**	**V8+21 (±3)**	**V1+261 (±7)**	**V1+321 (±7)**	**V1+506 (±7)**	**N/A**	**N/A**
Randomization		X[e]															
Vaccination		X			X[p]				X[p]								
Monitor subject for 30 minutes following vaccination[q]		X			X				X								
Examine vaccination site[r]		X[s]		X	X[s]		X[d]		X[s]		X					X[d]	X[t]
AE/MAAE/PIMMC/ SAE assessment[u]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DC, diary card; eCRF, electronic case report form; EOS, end of study; ET, early termination; FDA, Food and Drug Administration; MAAE, medically attended adverse event; N/A, not applicable; PIMMC, potentially immune-mediated medical condition; SAE, serious adverse event; SUSAR, suspected unexpected serious adverse reaction; ULN, upper limit of normal; Unsch, unscheduled; V, visit; WOCBP, women of childbearing potential.

[a] Telephone call assessment.

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

[c] Vital sign measurements include oral temperature, pulse rate, and blood pressure. Vital signs will be measured before blood is collected, at both pre-vaccination and 30±5-minute postvaccination time points on a vaccination day. Diastolic and systolic blood pressure will be measured after the subject is seated for at least 5 minutes.

[d] If clinically indicated.

[e] Prior to vaccination.

[f] Ask subject a standard nonleading question to elicit any medically related changes in their well-being. Ask if they have been hospitalized, had any accidents, used any new medications, received any vaccinations, or changed concomitant medication regimens (both prescription and over-the-counter medications).

[g] Diary Card I (Days 1-8), III (Days 22-29), and V (Days 142-149) will be used to collect unsolicited and solicited local and systemic reactions. Diary Card II (Days 9-21), IV (Days 30-43), VI (Days 150-163) will be used to collect unsolicited AEs.

[h] If applicable, according to the protocol period, collect and review DC with subject.

[i] Use of all concomitant medications that the subject is taking at the time of Visit 1, medications taken up to 14 days prior to Visit 1, and vaccines received 12 months prior to Visit 1 will be recorded in the subject's eCRF.

[j] Obtained by interview and by review of diary card completed by the subject.

[k] Any physical examination findings will be collected in the eCRF for medical history data presentation.

[l] Targeted physical examination will be performed at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities. Any findings from this examination will be collected in the eCRF for AEs.

[m] A urine pregnancy test must be performed within 24 hours prior to vaccination and pregnancy test results must be final and negative prior to vaccination.

[n] Hematology: complete blood count with differential, platelet count; coagulation: partial thromboplastin time and prothrombin time (international normalized ratio); chemistry/metabolic panel: ALT, AST, total bilirubin, creatinine, and blood urea nitrogen.

[o] For abnormal laboratory results that are clinically significant and for ALT and/or AST elevations ≥2.6 × ULN, repeat test until resolved or results become stable (see Section 6.2.5.8).

[p] Subjects with an acute illness, including body temperature greater than 100.4°F, immediately prior to each vaccination or, per subject report, within 3 days prior to a scheduled vaccination in this study can be rescheduled for vaccination as long as the vaccination visit is within the visit window. Subjects with a Grade ≥3 AE that has not returned to baseline or stabilized will not be revaccinated. Subjects with a serum ALT and/or AST elevation that is Grade 2 (moderate) or greater based on FDA toxicity grading (ie, ≥2.6 × ULN) will not be revaccinated unless the value resolves on repeat testing to the screening baseline value (ie, baseline toxicity score) and the subject remains within the visit window allowance (see Section 4.3).

[q] At Visits 1, 4, and 8, subjects will be monitored for solicited and unsolicited AEs, SAEs, MAAEs, PIMMCs, and SUSARs for at least 30 minutes after vaccination; concomitant medications will be recorded.

[r] Examine vaccination site for erythema/redness and swelling and monitor for pain.

[s] At Visits 1, 4, and 8, complete a 30±5-minute postvaccination injection site examination for erythema/redness and swelling and monitor for pain. If a visible injection-site abnormality is observed, document with a photograph.

[t] If the unscheduled visit occurs within 7 days after any of the study vaccinations.

[u] Only MAAEs, PIMMCs (see Appendix 2, Section 12.2), and SAEs will be collected after Day 163; all other AEs will be collected through 21 days following each vaccination.

12.2 Appendix 2: Potentially Immune-Mediated Medical Conditions

An adverse event of special interest (serious or nonserious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (eg, regulators) might also be warranted (based on Council for International Organizations of Medical Sciences VI).

For this study, adverse events of special interest will include the following list of PIMMCs:

Gastrointestinal disorders

- Autoimmune pancreatitis
- Celiac disease
- Crohn's disease
- Microscopic colitis
- Ulcerative colitis
- Ulcerative proctitis

Liver disorders

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

Metabolic diseases

- Addison's disease
- Autoimmune hypophysitis
- Autoimmune thyroiditis (including Hashimoto thyroiditis)
- Diabetes mellitus type I

- Grave's or Basedow's disease

Musculoskeletal disorders

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

Neuroinflammatory disorders

- Acute disseminated encephalomyelitis, including site-specific variants (eg, noninfectious encephalitis, encephalomyelitis, myelitis, radiculomyelitis)
- Cranial nerve disorders, including paralyses/paresis (eg, Bell's palsy)
- Guillain-Barré syndrome, including Miller Fisher syndrome and other variants
- Immune-mediated peripheral neuropathies and plexopathies, including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy
- Multiple sclerosis
- Narcolepsy

- Optic neuritis
- Transverse myelitis
- Myasthenia gravis, including Eaton-Lambert syndrome

Skin disorders

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

Vasculitides

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

Others

- Antiphospholipid syndrome
- Autoimmune hemolytic anemia

- Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis)
- Autoimmune myocarditis/cardiomyopathy
- Autoimmune neutropenia
- Autoimmune pancytopenia
- Autoimmune thrombocytopenia
- Goodpasture syndrome
- Idiopathic pulmonary fibrosis
- Pernicious anemia
- Polyglandular autoimmune syndrome
- Raynaud's phenomenon
- Sarcoidosis
- Sjögren's syndrome
- Stevens-Johnson syndrome
- Uveitis

12.3 Appendix 3: US FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (a partial list)

http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf

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
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 Signs[a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C)[b]	38.0-38.4	38.5-38.9	39.0-40	>40
(°F)[b]	100.4-101.1	101.2-102.0	102.1-104	>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

Abbreviation: ER, emergency room.

[a] Subject 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 judgement when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C)[a]	38.0-38.4	38.5-38.9	39.0-40	>40
(°F)[a]	100.4-101.1	101.2-102.0	102.1-104	>104
Chills[b]	Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual and social functional activities	Symptoms causing inability to perform usual social and functional activities	Not applicable
Arthralgia[b]	Joint pain causing no or minimal interference with usual and social functional activities	Joint pain causing greater than minimal interference with usual and social functional activities	Joint pain causing inability to perform usual and social and functional activities	Disabling joint pain causing inability to perform basic self-care functions
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 loose 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 daily activity	Some interference with daily 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

Abbreviations: ER, emergency room; IV intravenous.

[a] Oral temperature; no recent hot or cold beverages or smoking. (Note, this same information is also provided in Vital Signs table above.)

[b] Definition from Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases (US). Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events. Version 2.1, July 2017 [35 screens]. Available from http://rsc.tech-res.com/docs/default-source/safety/division-of-aids-(daids)-table-for-grading-the-severity-of-adult-and-pediatric-adverse-events-corrected-v-2-1.pdf?sfvrsn=2.

Serum[a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)[b]
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
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

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; 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).

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[b]	1.11-1.20 × ULN	1.21-1.25 × ULN	>1.25 ULN
PTT – increase by factor	1.0-1.2 × ULN	1.21-1.4 × ULN	1.41-1.5 × ULN	>1.5 ULN

Abbreviations: 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.

[b] ULN is the upper limit of the normal range.

12.4 Appendix 4: Protocol Amendments and Version Updates

The original Protocol Version 1.0 was dated 19 October 2017. Additions to the study protocol are shown in **bold** and deletions are shown in ~~strike through~~ text. Corrections of obvious typing errors or omissions and other editorial changes are not highlighted.

12.4.1 Protocol Version 1.1 (Typographical Error Correction)

Change Number 1

The secondary immunogenicity objectives were corrected to accurately reflect the Day 142 time point for the relevant assessments.

Reason

This correction was typographical.

Protocol Section

Synopsis – Objectives; Section 2.2.2 – Secondary Immunogenicity Objectives

Change to or Section Deleted:

Synopsis – Objectives; Section 2.2.2 – Secondary Immunogenicity Objectives

- To assess the serum HAI antibody titers, SPRs, and seroconversion rates (SCRs) against each vaccine strain in the study through Day ~~163~~ **142** of the prime-boost vaccination series.
- To assess the serum HAI antibody titers, SPRs, and SCRs against each vaccine strain in the study through Day 262 of the prime prime-boost vaccination series.
- To assess the serum microneutralization (MN) antibody titers and SCRs against each vaccine strain in the study through Day ~~163~~ **142** of the prime-boost vaccination series.
- To assess the serum MN antibody titers and SCRs against each vaccine strain in the study through Day 262 of the prime-prime-boost vaccination series.

12.4.2 Protocol Version 1.2

Change Number 1

The PPD Medical Monitor changed.

Reason

The new medical monitor's name and position were included.

Protocol Section

Cover page

Change to or Section Deleted:

Medical Monitor: ~~Michael Barri~~ **John Sanders**, MD
Associate Medical Director, PPD

Change Number 2

The IND number was added to the protocol.

Reason

The IND number became available.

Protocol Section

Cover page

Change to or Section Deleted:

IND Number: **17929**

Change Number 3

The "A" designation was removed from A(H5) influenza throughout the protocol, except for the title of the study.

Reason

The removal of the "A" was for simplification of the text and does not affect meaning.

Protocol Section

Global

Change to or Section Deleted:

All references to A(H5) influenza changed to H5.

Change Number 4

Potentially immune-mediated medical conditions were separated from medically attended adverse events in order to collect each event as a separate entity.

Reason

This update was made for accuracy of data collection and presentation.

Protocol Section

Global

Change Number 5

Secondary safety objectives were clarified to accurately reflect the duration of AE collection.

Reason

The change was made to increase clarity of the defined time points for AE assessments.

Protocol Section

Synopsis – Secondary Safety Objectives; Section 2.2.1 – Secondary Safety Objectives; Section 7.2 – Secondary Endpoints

Change to or Section Deleted:

Synopsis – Secondary Safety Objectives

- To assess the occurrence of serious adverse events**,** ~~and~~ medically attended adverse events (MAAEs**), and potentially immune-mediated medical conditions (PIMMCs;** see Appendix 2, Section 12.2) ~~including a subset of specific potentially immune-mediated medical conditions (PIMMCs)~~ in the 12 treatment groups ~~for~~ **through** 12 months after the last dose of study vaccine ~~and to~~**.**
- **To** assess the occurrence of unsolicited adverse events for 21 days after ~~the last~~ **each** dose of study vaccine.

Section 2.2.1 – Secondary Safety Objectives

- To assess the occurrence of SAEs**,** ~~and~~ medically attended adverse events (MAAEs**), and potentially immune-mediated medical conditions (PIMMCs;** see Appendix 2, Section 12.2) ~~including a subset of specific potentially immune-mediated medical conditions (PIMMCs)~~ in the 12 treatment groups ~~for~~ **through** 12 months after the last dose of study vaccine ~~and to~~**.**
- **To** assess the occurrence of unsolicited AEs for 21 days after ~~the last~~ **each** dose of study vaccine.

Section 7.2 – Secondary Endpoints

- Occurrence of SAEs**,** ~~and the occurrence of~~ MAAEs, ~~including a subset of specific~~ **and** PIMMCs in 12 treatment groups ~~for~~ **through** 12 months after the last dose of study vaccine

Change Number 6

Objective revised for clarity.

Reason

Level of detail not needed here.

Protocol Section

Section 2.3 – Exploratory Immunogenicity Objectives

Change to or Section Deleted:

- To assess peripheral antibody responses to epitopes within the influenza virus surface proteins HA or neuraminidase induced by prime-boost or prime-prime-boost vaccination series~~administered IM with AS03 or MF59 adjuvant 21 days apart or 141 days apart~~.

Change Number 7

Protocol exclusion criterion changed.

Reason

The change was made to increase clarity of timing for the urine pregnancy test.

Protocol Section

Synopsis – Exclusion Criteria; Section 4.1.2 – Exclusion Criteria

Change to or Section Deleted:

Synopsis – Exclusion Criteria; Section 4.1.2 – Exclusion Criteria

2. A woman who has a positive urine pregnancy test ~~within 24 hours~~ prior to vaccination in this study or a woman who is breastfeeding.

Change Number 8

Clarification regarding the responsibilities of the independent data monitoring committee.

Reason

The IDMC meeting frequency was changed from ad hoc to only if a pausing rule is met.

Protocol Section

Synopsis – Statistical Methods; Section 3.1 – Study Design; Section 10.1.5 – Independent Data Monitoring Committee

Change to or Section Deleted:

Synopsis – Statistical Methods

No formal independent data monitoring committee meetings are planned for this study. **The independent data monitoring committee will meet only if a pausing rule is met**. ~~Ad hoc meetings may occur for any immediate concerns that are observed~~.

Section 3.1 – Study Design

No formal independent data monitoring committee (IDMC) meetings are planned for this study. **The IDMC will meet only if a pausing rule is met**. ~~Ad hoc meetings may occur for any immediate concerns that are observed~~.

Section 10.1.5 – Independent Data Monitoring Committee

The IDMC will operate according to the IDMC Charter ~~and will monitor safety information on this study on an ad hoc basis~~. **The IDMC will review study progress and oversee clinical, safety, and reactogenicity data on an ad hoc basis; the IDMC will meet only if a pausing rule is met.** The IDMC will be composed of 3 members with expertise in the conduct and safety oversight of vaccine clinical studies. One of the IDMC members will serve as the IDMC chairperson.

~~An IDMC will review study progress and oversee clinical, safety, and reactogenicity data on an ad hoc basis; ad hoc meetings may occur for any immediate concerns that are observed.~~

Change Number 9

Detail was provided to identify study staff blinding procedures.

Reason

Original text was not sufficiently clear as to blinding assignments at study sites.

Protocol Section

Synopsis – Study Design; Section 3.1 – Study Design

Change to or Section Deleted:

Synopsis – Study Design; Section 3.1 – Study Design

Study staff **not involved in investigational product (IP) preparation and administration** will be blinded to unique group assignment.

Change Number 10

Revised number of sites that will collect PBMC samples.

Reason

Original text was specific to number of sites; revised to present more general number of sites.

Protocol Section

Section 3.1 – Study Design

Change to or Section Deleted:

Section 3.1 – Study Design

~~At least 4~~ **A select number** of ~~the 6~~ sites will have capability for PBMC collections, and only **subjects enrolled at** those sites will ~~be assigned to subjects who~~ contribute to the PBMC subset.

Change Number 11

Revised description for clarity.

Reason

Further detail needed.

Protocol Section

Section 3.1.3 – Study Pausing Rules

Change to or Section Deleted:

Study pausing rules will be monitored throughout the study by the medical monitor. The sponsor will pause study enrollment and study vaccine administration and the IDMC will review unblinded safety data if any of the following are met:

Change Number 12

Revised future investigations list.

Reason

Removed a subject question from study design.

Protocol Section

Section 3.1.4 – Future Investigations

Change to or Section Deleted:

3. ~~Permission to take a photograph of a visible injection site abnormality for the purpose of medical management and safety evaluations.~~

Change Number 13

Revised exclusion criterion for clarity.

Reason

Original text was reassessed and needed rewriting.

Protocol Section

Synopsis – Exclusion Criteria; Section 4.1.2 – Exclusion Criteria

Change to or Section Deleted:

Synopsis – Exclusion Criteria; Section 4.1.2 – Exclusion Criteria

22. Has any condition that would, in the opinion of the investigator, place him or her at an unacceptable risk of injury or render him or her unable to meet the requirements of the protocol (including ~~tattoos or scars on the skin where the vaccine is to be administered~~site of injection reactogenicity assessments).

Change Number 14

Placement of revaccination text was revised.

Reason

This correction was made to move revaccination eligibility criteria to a more appropriate location in the protocol.

Protocol Section

Section 5.2.1 – Revaccination Eligibility

Change to or Section Deleted:

~~Subjects with a Grade ≥2 AE that has not returned to baseline or stabilized will not be revaccinated.~~

~~Subjects with an acute illness, including body temperature greater than 100.4°F immediately prior to a scheduled vaccination or, per subject report, within 3 days prior to a scheduled vaccination in this study can be rescheduled for vaccination as long as the vaccination visit is within the visit window.~~

Section 4.3 Revaccination Eligibility

Subjects are free to withdraw from further study vaccination at any time upon request. A subject may not be eligible to receive further study vaccination for any of the following reasons:

1. Does not meet the protocol inclusion or exclusion criteria at the time of the second or, if applicable, third vaccination.

2. Noncompliance with the protocol.

3. Serious or intolerable AE(s) that in the investigator's opinion precludes further study vaccination.

4. Laboratory safety assessment that remains clinically significant prior to planned vaccination.

5. Symptoms or an intercurrent illness not consistent with the protocol requirements or that justifies no further study vaccination.

6. Other (eg, pregnancy, development of contraindications precluding further study vaccination).

All subjects who discontinue from study treatment prematurely will follow the same visit schedule as other subjects.

Change Number 15

Revision to clarify allowed influenza vaccinations in study.

Reason

Prior paragraph was not clear.

Protocol Section

Section 5.7 – Prior Vaccinations and Concomitant Medications

Change to or Section Deleted:

Section 5.7 – Prior Vaccinations and Concomitant Medications

Sites may contact the medical monitor regarding use of concomitant medications prior to enrollment for guidance as necessary. If it is discovered that a subject is using a prohibited concomitant medication after he or she is enrolled in the study, the site should contact the medical monitor to resolve the situation. All instances of use of prohibited concomitant medications must be documented in the eCRF. All vaccinations obtained outside of the study itself will be recorded while the subject is enrolled. ~~Should a subject inadvertently receive a live seasonal influenza vaccination that interferes with the window of vaccination free period~~

~~prior to any trial vaccination, that vaccination can be withheld until the appropriate time has passed. Such a subject will not be deemed out of compliance or out of study visit window. All future visits will be adjusted accordingly.~~

Change Number 16

Paragraph rewritten for clarity.

Reason

Details in paragraph did not align with exclusion criteria details.

Protocol Section

Section 5.7.1 – Prohibited Prior and Concomitant Medications

Change to or Section Deleted:

Section 5.7.1 – Prohibited Prior and Concomitant Medications

Immunosuppression as a result of an underlying illness or treatment or the use of anticancer chemotherapy or radiation therapy (cytotoxic) within the preceding 36 months prior to **Day 1 (first vaccination)**~~screening~~ is prohibited.

Change Number 17

Paragraph rewritten for clarity.

Reason

Details in paragraph did not align with permitted medication guidelines.

Protocol Section

Section 5.7.2 – Permitted Prior and Concomitant Medication

Change to or Section Deleted:

Section 5.7.2 – Permitted Prior and Concomitant Medication

Prohibited concomitant medication ~~deemed necessary for the welfare of the subject~~ during the study may be given at the discretion of the investigator **if deemed in the best interest of the subject's health**. ~~However, i~~**I**t is the responsibility of the investigator to ensure that details regarding the medication will be recorded in full in the eCRF.

Change Number 18

Text rewritten for clarity.

Reason

Change made to align with schedule of events.

Protocol Section

Section 6.2.2 – Postvaccination Evaluation

Change to or Section Deleted:

Section 6.2.2 – Postvaccination Evaluation

At Visits 1 and 4 (Groups A-D, G-J) and at Visits 1, 4, and 8 (Groups E, F, K, L), subjects will be monitored for solicited (Section 6.2.5.2) and unsolicited AEs, SAEs, ~~and~~ MAAEs**, PIMMCs, and serious and suspected unexpected adverse reactions** (**SUSARs)** for at least 30 minutes after vaccination.

Change Number 19

Platelet count was added to the hematology profile.

Reason

This correction was due to an omission.

Protocol Section

Section 6.2.4 – Clinical Safety Laboratory Tests; Table 12-1; Table 12-2

Change to or Section Deleted:

Section 6.2.4 – Clinical Safety Laboratory Tests

Clinical safety laboratory tests will include the following according to Table 12-1 and Table 12-2:

- hematology: complete blood count with differential **and platelet count**.

Table 12-1; Table 12-2

[n] Hematology: complete blood count with differential**, platelet count**; coagulation: partial thromboplastin time and prothrombin time (international normalized ratio); chemistry/metabolic panel: alanine aminotransferase, aspartate aminotransferase, total bilirubin, creatinine, and blood urea nitrogen.

Change Number 20

Definitions added for clarity.

Reason

Definitions of MAAEs and PIMMCs not provided in last version of the document.

Protocol Section

Section 6.2.5.1 – Definitions of Adverse Events

Change to or Section Deleted:

Medically attended AEs are defined as AEs with medically attended visits, including hospital, emergency room, urgent care clinic, or other visits to or from medical personnel (medical doctor, physician assistant, nurse practitioner) for any reason.

Potentially immune-mediated medical conditions are considered unexpected events and should be reported as adverse events of special interest. The PIMMCs of concern for this study are detailed in Appendix 2, Section 12.2.

Change Number 21

Details of laboratory findings that qualified as AEs were corrected to accurately represent intended grading and assessment process.

Reason

Original text was not clear in regard to clinical significance and Toxicity Grading Scale.

Protocol Section

Section 6.2.5.3 – Assessing and Documenting Adverse Events; Section 6.2.5.5 – Assessment of Severity; Section 6.2.5.8 – Follow-up of Subjects Reporting Adverse Events

Change to or Section Deleted:

Section 6.2.5.3 – Assessing and Documenting Adverse Events

Laboratory findings that qualify as AEs and nonqualifying laboratory abnormalities outside the laboratory's reference range will be toxicity graded according to the FDA Toxicity Grading Scale (Appendix 3, Section 12.3). ~~Any~~ **Similarly, vital signs outside the clinic reference range will be graded according to the same scale. The toxicity grade for each identified laboratory finding and out-of-reference range vital sign will be documented in the study dataset.**

The investigator will assess each Toxicity Scale Grade 1 ~~and Grade 2~~**-4 finding and determine whether the finding is** clinically significant ~~observations and all hematology~~, ~~coagulation, or serum chemistry/metabolic panel results that are at least~~. **Grade 1-3 clinically significant findings will be categorized as AEs. All** Grade ~~3 (irrespective~~ **4 findings (regardless** of **investigator**-assessed clinical significance) ~~that occurs after vaccination~~ will be ~~recorded~~ **graded** as ~~an AE~~ **AEs**. Other safety assessments (eg, vital sign measurements), or those identified from review of other documents (eg, diary card), including those that worsen from baseline, or are felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as AEs or SAEs.

For a laboratory ~~assessment~~ **finding** assessed as an AE (see above), the investigator should report a medical condition rather than the name of the laboratory test abnormality whenever

possible. For example, ~~for~~ **if the subject has** a clinically significant Grade 1~~/Grade~~**,** 2**,** or ~~Grade~~ 3 increased white blood cell count ~~was~~ due to bronchitis, then the investigator should report the medical condition of "bronchitis" rather than "high white blood cell count." Similarly, a **clinically significant** decreased hemoglobin should be reported as "anemia" rather than "low hemoglobin," and a **clinically significant** decreased platelet count should be reported as "thrombocytopenia" rather than "low platelets."

~~The severity of solicited AEs will be classified. Laboratory findings that qualify as AEs and nonqualifying laboratory abnormalities outside the laboratory's reference range will be toxicity graded according to the FDA Toxicity Grading Scale (Appendix 3, Section 12.3). This grading is distinct from and does not translate directly to the AE grading by the investigator, which is based on clinical judgment.~~

Section 6.2.5.5 – Assessment of Severity

~~Laboratory abnormalities (hematology and serum chemistries) that are abnormal will be entered into the AE reporting page only if the investigator determines there is clinical significance~~**. Grade 1-3 hematology or serum chemistry values determined by the investigator to be clinically significant will be entered into the AE reporting page. All Grade 4 laboratory findings are considered AEs regardless of the investigator's determination of clinical significance.**

Section 6.2.5.8 – Follow-up of Subjects Reporting Adverse Events

In the case of an abnormal laboratory value that is entered as an AE due to toxicity grade parameters (ie, clinically significant Grade 1 **to 3** or ~~above or any~~ Grade ~~3,~~**4 [regardless of clinical significance]),** the subject will be required to have a repeat laboratory test with results assessed by the investigator and continued monitoring as determined appropriate for the clinical situation.

Change Number 22

Clarification to identify types of AEs reported immediately to PPD and the length of time after the first vaccine dose that SAEs and PIMMCs will be collected was revised.

Reason

The MAAEs group was removed, as any AE that meets SAE criteria would include MAAEs. The length of time for event follow-up postvaccination was revised.

Protocol Section

Section 6.2.5.4 – Reporting Adverse Events

Change to or Section Deleted:

Section 6.2.5.4 – Reporting Adverse Events

Any AE that meets SAE or ~~MAAE~~ PIMMC criteria (Section 6.2.5.1 and Appendix 2, Section 12.2) must be reported to PPD immediately (ie, within 24 hours) after the time site personnel first learn about the event. The following contact information is to be used for SAE reporting:

SAE Hotline: [redacted]

SAE Fax line: [redacted]

The safety event reporting periods are shown in Figure 6-1 for Groups A to D **and G to J** and Figure 6-2 for Groups E, F, K, and L. Solicited AEs will be collected for 7 days after each vaccination. Unsolicited AEs will be collected for 21 days after each of 2 vaccine doses (Groups A-D and G-J) and for 21 days after each of 3 vaccine doses (Groups E, F, K, and L). Serious adverse events~~, MAAEs,~~ and PIMMCs will be collected for **approximately** 13 months after the first study vaccine dose (Groups A-D and G-J) and for **approximately** 17 months after the first study vaccine dose (Groups E, F, K, and L).

Change Number 23

Assessment of severity procedures revised.

Reason

Clarity regarding laboratory-related AEs was needed.

Protocol Section

Section 6.2.5.5 – Assessment of Severity

Change to or Section Deleted:

Section 6.2.5.5 – Assessment of Severity

The severity~~, or intensity,~~ of an AE refers to the extent to which an AE affects the subject's daily activities. All solicited AEs will be graded according to the FDA Toxicity Grading Scale (Appendix 3, Section 12.3) and entered into the AE reporting page. **Grade 1-3 hematology or serum chemistry values determined by the investigator to be clinically significant will be entered into the AE reporting page. All Grade 4 laboratory findings are considered AEs regardless of the investigator's determination of clinical significance. The severity of each** ~~Laboratory abnormalities (hematology and serum chemistries) that are abnormal will be entered into the AE reporting page only if the investigator determines there is clinical significance. For any clinically significant AEs that are entered into the AE eCRF, the intensity of the~~ AE will be rated as mild, moderate, or severe using the following criteria:

Change Number 24

Identification of analyses for immunogenicity-full analysis set.

Reason

Original text was not clear on what endpoint summaries would be performed.

Protocol Section

Section 7.5 – Analysis Sets

Change to or Section Deleted:

Section 7.5 – Analysis Sets

Immunogenicity-full analysis set (IFAS): The IFAS will consist of all subjects who are randomly assigned, receive at least 1 dose of IP, and have at least 1 valid postvaccination and determinate assay result. ~~Only~~**As supportive analysis, all** the ~~primary~~ immunogenicity

endpoint summaries will be performed on the IFAS ~~using treatment as~~ ~~randomized~~ **by actual treatments received**.

Change Number 25

Clarification needed regarding template standard text.

Reason

Respective obligations of sponsor and designee are clear without this text.

Protocol Section

Section 9.2 – Financial Disclosure

Change to or Section Deleted:

9.2 Financial Disclosure ~~and Obligations~~

~~Neither the sponsor nor PPD is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor PPD is financially responsible for further treatment of the subject's disease.~~

Change Number 26

Clarification needed regarding consistency of presentation in Table 12-1 and Table 12-2.

Reason

Same text should be used in both tables to define procedures.

Protocol Section

Table 12-1; Table 12-2

Change to or Section Deleted:

Table 12-1; Table 12-2

Removed "Review Diary Card" for Visit 1.

Table 12-2

Revised "Review diary card[g] ~~and toxicity grade for solicited reactions~~".

Change Number 27

Adverse event severity identification was corrected for global consistency.

Reason

This correction was made to be consistent with presentation of laboratory-related AE severity grade throughout the protocol.

Protocol Section

Table 12-1; Table 12-2

Change to or Section Deleted:

Table 12-1; Table 12-2

[p] Subjects with an acute illness, including body temperature greater than 100.4°F, immediately prior to each vaccination or, per subject report, within 3 days prior to a scheduled vaccination in this study can be rescheduled for vaccination as long as the vaccination visit is within the visit window. Subjects with a Grade ≥~~2~~**3** AE that has not returned to baseline or stabilized will not be revaccinated.

12.4.3 Protocol Amendment 1, Version 2.0

Additions to the study protocol are shown in **bold** and deletions are shown as ~~strikethrough~~ text. Administrative changes are not highlighted.

Change Number 1

Added text to indicate that subjects with US Food and Drug Administration (FDA) toxicity Grade 2 or greater (ie, ≥2.6 × upper limit of normal [ULN]) serum alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations should not receive revaccination, and provided guidance that FDA toxicity Grade 2 or greater ALT and/or AST elevations will be reported as an adverse event (AE).

Reason

Revaccination text was added based on feedback from the US FDA, and the associated AE text was added to ensure that FDA toxicity Grade 2 or greater ALT and/or AST elevations (≥2.6 × ULN) are appropriately identified.

Protocol Section

Section 4.2.1 – Reasons for Withdrawal/Discontinuation

4. A serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation that is Grade 2 (moderate) or greater based on FDA toxicity grading (ie, ≥2.6 × upper limit of normal [ULN]; see Appendix 3, Section 12.3) that does not resolve on repeat testing to the screening baseline value (eg, baseline toxicity score). (Note, subjects with elevated ALT and/or AST values cannot be revaccinated until resolution occurs [see Section 4.3].)

45. **Other** ~~L~~laboratory safety assessments that reveal Grade ≥3 hematological or biochemical values.

Section 4.3 – Revaccination Eligibility

4. A serum ALT or AST elevation that is Grade 2 (moderate) or greater based on FDA toxicity grading (ie, ≥2.6 × ULN; see Appendix 3, Section 12.3) regardless of

investigator-assessed clinical significance. Note, such an elevated ALT and/or AST value must be resolved on repeat testing to the screening baseline value (eg, baseline toxicity score) before revaccination can occur. Only those subjects who have resolution of the ALT and/or AST elevations within the visit window are eligible for revaccination.

~~4~~.5. **Other** ~~L~~laboratory safety assessment**s** that remain~~s~~ clinically significant prior to planned vaccination.

Section 6.2.5.3 – Assessing and Documenting Adverse Events

The investigator will assess each Toxicity Scale Grade 1-4 finding and determine whether the finding is clinically significant. Grade 1-3 clinically significant findings will be categorized as AEs. **An FDA toxicity Grade 2 (moderate) or greater (ie, ≥2.6 × ULN; see Appendix 3, Section 12.3) ALT and/or AST elevation (regardless of investigator-assessed clinical significance) will be entered into the AE reporting page.** All Grade 4 findings (regardless of investigator-assessed clinical significance) will be graded as AEs. Other safety assessments (eg, vital sign measurements), or those identified from review of other documents (eg, diary card), including those that worsen from baseline, or are felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as AEs or SAEs.

…

Any clinically significant safety assessment that is associated with an underlying disease **(unless explicitly identified above)**, unless judged by the investigator to be more severe than expected for the subject's condition, should not be reported as an AE.

Section 6.2.5.5 – Assessment of Severity

The severity of an AE refers to the extent to which an AE affects the subject's daily activities. All solicited AEs will be graded according to the FDA Toxicity Grading Scale (Appendix 3, Section 12.3) and entered into the AE reporting page. Grade 1-3 hematology or serum chemistry values determined by the investigator to be clinically significant will be entered into the AE reporting page. **An FDA toxicity Grade 2 (moderate) or greater (ie, ≥2.6 × ULN; see Appendix 3, Section 12.3) ALT and/or AST elevation (regardless of investigator-assessed clinical significance) will be entered into the AE reporting page,**

and the grading will be consistent with the FDA toxicity score. All Grade 4 laboratory findings are considered AEs regardless of the investigator's determination of clinical significance **and should also be entered using the FDA toxicity score for severity**. **In all other cases, t**~~T~~he severity of each AE will be rated as mild, moderate, or severe using the following criteria.

Section 6.2.5.8 – Follow-up of Subjects Reporting Adverse Events

All AEs must be reported in detail on the appropriate page in the eCRF and followed to satisfactory resolution, until the investigator deems the event to be chronic or not clinically significant, or until the subject is considered to be stable. In the case of an abnormal laboratory value that is entered as an AE due to toxicity grade parameters (ie, clinically significant Grade 1 to 3, Grade 4 [regardless of clinical significance], **and ALT and/or AST elevations ≥2.6 × ULN)**, the subject will be required to have a repeat laboratory test with results assessed by the investigator and continued monitoring ~~as determined appropriate for the clinical situation~~ **until the results return to the screening baseline value (ie, baseline toxicity score) or are considered stable with a new baseline. Subjects may not receive revaccination if ALT and/or AST elevations reach ≥2 by FDA toxicity score and do not return to the screening baseline value (ie, baseline toxicity score) by the time of revaccination**.

Table 12-1 – Schedule of Events, Groups A to D, G to J; and
Table 12-2 – Schedule of Events, Groups E, F, K, L

[o] For abnormal laboratory results that are clinically significant **and for ALT and/or AST elevations ≥2.6 × ULN**, repeat test until resolved or results become stable (see Section 6.2.5.8).

[p] Subjects with an acute illness, including body temperature greater than 100.4°F, immediately prior to each vaccination or, per subject report, within 3 days prior to a scheduled vaccination in this study can be rescheduled for vaccination as long as the vaccination visit is within the visit window. Subjects with a Grade ≥3 AE that has not returned to baseline or stabilized will not be revaccinated. **Subjects with a serum ALT and/or AST elevation that is Grade 2 (moderate) or greater based on FDA toxicity grading (ie, ≥2.6 × ULN) will not be revaccinated unless the value resolves on repeat testing to the screening baseline value (ie, baseline toxicity score) and the subject remains within the visit window allowance (see Section 4.3).**

Change Number 2

Adverse event severity grading definitions for fever, chills, and arthralgia were added to the FDA systemic reactions table in Appendix 3.

Reason

Solicited systemic reactions of fever, myalgia, arthralgia, fatigue, headache, nausea, vomiting, diarrhea, and chills are being collected in this study (as defined in Section 6.2.5.2). However, fever, chills, and arthralgia are not included in the FDA systemic events table. The additional guidance was added to the FDA systemic events table to ensure accuracy and consistency in the evaluation of these AEs during the study and as a resource to the study centers (so all information is in one location).

Protocol Section

Appendix 3: US FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (a partial list)

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C)[a]	**38.0-38.4**	**38.5-38.9**	**39.0-40**	**>40**
(°F)[a]	**100.4-101.1**	**101.2-102.0**	**102.1-104**	**>104**
Chills[b]	**Symptoms causing no or minimal interference with usual social and functional activities**	**Symptoms causing greater than minimal interference with usual and social functional activities**	**Symptoms causing inability to perform usual social and functional activities**	**Not applicable**
Arthralgia[b]	**Joint pain causing no or minimal interference with usual and social functional activities**	**Joint pain causing greater than minimal interference with usual and social functional activities**	**Joint pain causing inability to perform usual and social and functional activities**	**Disabling joint pain causing inability to perform basic self-care functions**
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 loose 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 daily activity	Some interference with daily 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

Abbreviations: ER, emergency room; IV intravenous.

[a] **Oral temperature; no recent hot or cold beverages or smoking. (Note, this same information is also provided in Vital Signs table above.)**

[b] **Definition from Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases (US). Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events. Version 2.1, July 2017 [35 screens]. Available from http://rsc.tech-res.com/docs/default-source/safety/division-of-aids-(daids)-table-for-grading-the-severity-of-adult-and-pediatric-adverse-events-corrected-v-2-1.pdf?sfvrsn=2.**