STATISTICAL ANALYSIS PLAN

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

BP-I-23-001

NCT#:	NCT06560151
COMPOUNDS:	Influenza vaccine antigens: Egg-A/Astrakhan/3212/2020 (H5N8) (Sanofi Pasteur Inc.) Egg-A/bar-headed goose/Qinghai Lake/1A/2005 (H5N1) (Sanofi Pasteur Inc.) Adjuvants: AS03A (GSK) MF59 (CSL Seqirus)
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ACKNOWLEDGEMENT AND SIGNATURE SHEET

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1. LIST OF ABBREVIATIONS

Table 1: Abbreviations

Abbreviation	Explanation
ADaM	Analysis Data Model
AE	Adverse event
ATC	Anatomical therapeutic chemical
BARDA	Biomedical Advanced Research and Development Authority
BMI	Body mass index
CI	Confidence interval
cm	Centimeter
CRF	Case report form
CSR	Clinical Study Report
CTMS	Clinical Trial Management System
DMP	Data Management Plan
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMT	Geometric mean titer
HAI	Hemagglutination-inhibition
HEENT	Head, eyes, ears, nose, and throat
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ID	Identifier
IFAP	Immunogenicity full analysis population
IPPP	Immunogenicity per protocol population
kg	Kilogram
LLOQ	Lower limit of quantitation
m^2	Meter squared
MAAE	Medically attended adverse event
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
mL	Milliliter

Abbreviation	Explanation
mmHg	Millimeters of mercury
MN	Microneutralization
pIMD	Potentially immune-mediated disease
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAR	Suspected Adverse Reaction
SD	Standard deviation
SDTM	Study Data Tabulation Model
SMC	Safety Monitoring Committee
SOC	System organ class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent adverse event
TLF	Table, listing, and figure
ULOQ	Upper limit of quantification
WHO	World Health Organization

2. PURPOSE OF THE ANALYSES

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and data displays to be included in the interim analysis and Clinical Study Report (CSR) for Protocol BP-I-23-001. This document provides details on study populations, how the variables will be derived, how missing data will be handled and details on statistical methods to be used to analyze the safety and efficacy data.

The SAP is based on ICH guidelines E3 (Structure and Content of Clinical Study Reports), E9 (Statistical Principles for Clinical Trials), and E9 (R1) (Addendum: Estimands and Sensitivity Analysis in Clinical Trials).

The document may evolve over time, for example, to reflect the requirements of protocol amendments or regulatory requests. However, the final SAP must be finalized, approved by BARDA, and placed on file before the database is locked. If differences occur between analyses described in the SAP and the current protocol, those found in this SAP will assume primacy. Deviations from the final approved plan will be noted in the CSR. Table, listing, and figure (TLF) shells are provided in separate documents.

3. PROTOCOL SUMMARY

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

Names of Investigational Products:

Influenza vaccine antigens:

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

Adjuvants:

- AS03A (GSK)
- MF59 (CSL Seqirus)

Names of Active Ingredients:

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

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

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

Protocol Number: BP-I-23-001

Version Number: 3.0

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

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

Study Objectives:

<u>Primary Objectives</u>

Safety

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

Immunogenicity

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

Secondary Objectives

Safety

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

Immunogenicity

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

Methodology:

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

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

Antigen*	Adjuvant	Antigen Dose	Treatment Group	# of Participants	
				18-64 y	≥65 y
Egg-A/Astrakhan/3212/2020 (H5N8)	AS03A Full Dose	3.75 µg	A	60	0
		7.5 µg	B	60	60
		15 µg	C	60	60
Egg-A/Astrakhan/3212/2020 (H5N8)	AS03A Half Dose	3.75 µg	D	60	0
		7.5 µg	E	60	60
		15 µg	F	60	60
	MF59	3.75 µg	G	60	0

Egg-A/Astrakhan/3212/2020 (H5N8)		7.5 µg	H	60	60
		15 µg	I	60	60
Egg-A/bar-headed goose/Qinghai Lake/1A/2005 (H5N1)	AS03A Full Dose	3.75 µg	J	60	0
		7.5 µg	K	60	60
		15 µg	L	0	60
Egg-A/bar-headed goose/Qinghai Lake/1A/2005 (H5N1)	MF59	3.75 µg	M	60	0
		7.5 µg	N	60	60
		15 µg	O	0	60

*All antigens are manufactured by Sanofi.

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

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

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

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

Diagnosis and main criteria for inclusion:

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

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

Screening Criteria

Participant Inclusion Criteria

1. Male or non-pregnant female, 18 years of age or older at the time of screening and informed consent.
2. Willing and able to provide written informed consent prior to initiation of study procedures.
3. Agrees to have specimens collected during this trial specifically for the purpose of future research stored for future research use.
4. In relatively stable health, as determined by medical history and physical examination.
    a. Any chronic medical diagnoses or conditions should be stable and well managed, with no significant changes expected during the study period, and in the opinion of the site

investigator, will not impact the ability to assess safety and/or immunogenicity per the study design.

2. If a female of childbearing potential[a] who is sexually active, agrees to use an adequate method of birth control[b] from Screening through 4 weeks following the last study vaccination and has used an adequate birth control method for at least 2 months prior to Screening.
    a. Female of childbearing potential is defined as post onset menarche and pre-menopausal person capable of becoming pregnant. This does not include females who meet any of the following conditions: a) menopausal >2 years; b) tubal ligation >1 year; c) bilateral salpingo-oophorectomy; or d) hysterectomy.
    b. Adequate contraception is defined as a contraceptive method with a failure rate of less than 1% per year when used consistently and correctly and when applicable, in accordance with the product label, for example: oral contraceptives, either combined or progestogen alone; injectable progestogen; implants of etonogestrel or levonorgestrel; estrogenic vaginal ring; percutaneous contraceptive patches; intrauterine device or intrauterine system; the female participant has exclusively female sexual partners; male partner is sterile or otherwise unable to produce sperm (information on the person's sterility can come from the site personnel's review of the participant's medical records or interview with the participant regarding her medical history); male condom combined with a vaginal spermicide (foam, gel, film, cream, or suppository); or male condom combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, film, cream, or suppository).
3. Available for all study visits, willing to participate in all study procedures, and not planning to relocate from the area for the duration of the study.

Participant Exclusion Criteria

1. Has an acute illness, as determined by the site investigator, within 72 hours prior to vaccination.
    a. An acute illness that is nearly resolved, with only minor residual symptoms remaining, is allowable if, in the opinion of the site investigator, the residual symptoms will not interfere with the ability of study staff to assess safety parameters as required by the protocol.
2. Has a history of severe reaction to any influenza vaccine.
3. Has a known allergy to squalene-based adjuvants.
4. Female of childbearing potential who has a positive urine pregnancy test or who is currently breastfeeding.
5. Has a body mass index >35 kg/m^2.
6. Has known human immunodeficiency virus, hepatitis B, or hepatitis C infection (based on medical history).
7. Has a history of any pIMDs (list provided in Protocol Appendix 3), neuralgia, paresthesia, neuritis, convulsions, or encephalomyelitis within 90 days prior to Screening, or a family history of Guillain-Barré syndrome.
8. Has narcolepsy or a first degree relative with narcolepsy.
9. Has a history of alcohol or drug abuse within 5 years prior to Screening.

10. Has any diagnosis, current or past, of schizophrenia, bipolar disease, or any other psychiatric diagnosis that may, in the opinion of the site investigator, interfere with participant compliance or safety evaluations.
11. Is immunosuppressed due to an underlying disease or medication, use of anticancer chemotherapy (cytotoxic), or radiation therapy.
12. With the exception of basal or squamous cell skin cancer, has known active neoplastic disease, including hematologic malignancy.
13. Has long-term use (≥14 consecutive days) of glucocorticoids including oral or parenteral prednisone or prednisone equivalent (>20 mg total dose per day) or high-dose inhaled steroids (>800 µg/day of beclomethasone dipropionate or equivalent) within 1 month prior to screening in this study. However, participants on low-dose inhaled steroids (≤800 µg/day of beclomethasone dipropionate or equivalent) or topical steroids are not excluded.
14. Has received immunoglobulin or other blood product (with the exception of Rho[D] immune globulin) within the 90 days prior to screening in this study.
15. Has received any (licensed or under Emergency Use Authorization [EUA]) live vaccines within 4 weeks or inactivated, messenger RNA (mRNA), or recombinant protein vaccines within 2 weeks prior to screening, or plans to receive such vaccines (including seasonal influenza and COVID-19 vaccines) from screening through 22 days following the second dose of the study vaccine, inclusive of the vaccination day (Screening Visit through Day 43).
16. Is participating or plans to participate in another interventional clinical trial (either active or follow-up phase) during the study period.
17. Has participated in an A(H5) influenza vaccine study in the past or has a history of A(H5) influenza infection prior to vaccination in this study. This includes, but is not limited to, influenza sub-types A(H5N1), A(H5N8), and A(H5N6).
18. Has any laboratory test result or clinical findings (including vital signs) that singly or in combination are likely to unfavorably alter the risks of participant participation or to confound study safety or immunogenicity results, in the opinion of the site investigator. Additionally, the following are exclusionary:
    a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 times the upper limit of normal (ULN), or
    b. Bilirubin >1.5 times the ULN unless isolated Gilbert's syndrome.
19. Has any disease or medical condition that, in the opinion of the site investigator, might confound interpretation of safety or immunogenicity.

Vaccination Eligibility Criteria

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

The most recent laboratory and vital sign results will be used when determining eligibility for the second vaccination. Any abnormal laboratory results that would be exclusionary or could be

considered clinically significant should be followed up as soon as possible by resampling at an Unscheduled Visit. An acceptable result upon resampling may replace the previous abnormal laboratory result for purposes of evaluating the Vaccination Eligibility Criteria.

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

Inclusion Criteria for Vaccination Eligibility

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

Exclusion Criteria for Vaccination Eligibility

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

Investigational product, dosage and mode of administration:

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

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

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

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

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

Duration of treatment:

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

Reference therapy, dosage and mode of administration: Not applicable

Criteria for evaluation:
Immunogenicity

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

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

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

Safety

Safety will be evaluated by assessing frequency and severity of solicited local and systemic reactogenicity symptoms occurring within 8 days following each vaccination, inclusive of the vaccination day (Day 1 through Day 8 and Day 22 through Day 29), unsolicited TEAEs occurring within 22 days following each vaccination, inclusive of the vaccination day (Day 1 through Day 22 and Day 22 through Day 43), and treatment-emergent SAEs, MAAEs, and pIMDs occurring during study participation (through Day 203). Safety assessments will also include physical examination, vital signs, and clinical laboratory tests (hematology and chemistry).

Study Endpoints:

Primary Endpoints

Primary Safety Endpoints:

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

Primary Immunogenicity Endpoint

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

Secondary Endpoints

Secondary Safety Endpoints

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

Secondary Immunogenicity Endpoints

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

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

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

Statistical methods:

Analysis Plan

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

Interim Analysis

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

Ad Hoc Safety Monitoring Committee (SMC) Meeting

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

Final Analyses

The final analyses will include all safety and immunogenicity data through the end of study. The study database will be monitored and cleaned per the associated study plans. Study data will be unblinded to prepare the final analyses. Cumulative summaries of all SAEs, MAAEs, and pIMDs

occurring from Day 1 through the end of study will be included. Further details will be specified in the SAP.

Analysis Populations

Safety Population

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

Immunogenicity Full Analysis Population

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

Immunogenicity Per Protocol Population

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

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

All immunogenicity analyses will also be performed on the IPPP.

4. GENERAL ANALYSIS AND REPORTING CONVENTIONS

The following is a list of general analysis and reporting conventions to be applied for this study:

- Validation and quality control of Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) datasets, tables, listings, and figures will be performed as specified in the Statistical Validation and Quality Control Plan.
- Categorical variables will be summarized using counts (n) and percentages (%) and will be presented in the form n (%). Percentages will be rounded to one decimal place. If n=0, then no percent will be shown. To ensure completeness, all summaries for categorical and discrete variables will include all reportable categories, even if none of the participants had a response in a particular category.
- Numeric variables will be summarized using n, mean, standard deviation (SD), median, minimum (min), and maximum (max). For variables summarized using geometric means, the back-transformed SD will be presented. The min/max will be reported at the same level of significance as original data. The mean and median will be reported at one more significant digit than the precision of the data. SD will be reported at two more significant digits than the precision of the data. The level of precision may be modified on specific displays based on clinical judgement.
- The median will be reported as the average of the two middle numbers if the dataset contains an even number of observations.
- Confidence intervals (CIs) will be presented as 95% exact (Clopper-Pearson) or asymptotic CIs.
- Test statistics including t and z test statistics will be reported to two decimal places.
- P-values will be reported to 3 decimal places if greater than or equal to 0.001. If less than 0.001 then report ‘<0.001’. Report p-values and significant levels as 0.05 rather than .05. A p-value can be reported as “1.000” only if it is exactly 1.000 without rounding. A p-value can be reported as “0.000” only if it is exactly 0.000 without rounding.
- No preliminary rounding should be performed; rounding should only occur after analysis. To round, consider the digit to right of last significant digit: if < 5 then round down, if >=5 then round up.
- In general, listings will be displayed by treatment group and participant and will be sorted in the order that columns are displayed, starting with the first column on the left.
- All analyses will be performed using the SAS System version 9.4 or higher. Figures will be programmed using SAS version 9.4 or higher or R version 3.4.1 or higher.
- Dates will be displayed as DDMMMYYYY (e.g., 31May2023).
- Calculations using dates will be performed as noted below.

  Visit 1 Date = Day 1

  Study day for dates after Visit 1/Day 1

Study Day = Date – Visit 1 Date + 1

Study day for dates prior to Visit 1/Day 1

Study Day = Date – Visit 1 Date

Total duration of days

Duration = End Date – Start Date + 1

Note: no calculation will be needed for age as it will be pulled directly from the clinical database.

- For data collected at both the Screening Visit and prior to vaccine administration on Visit 1/Day 1, baseline will be defined as the latest non-missing value collected prior to vaccine administration. Otherwise, if data are collected at only the Screening Visit or Visit 1/Day 1, the collected value will be considered the baseline value for analyses.

If departures from these general conventions are present in the specific evaluation section of this SAP, then those conventions will take precedence over these general conventions.

5. ANALYSIS POPULATIONS

5.1. Safety Population

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

5.2. Immunogenicity Full Analysis Population

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

5.3. Immunogenicity Per Protocol Population

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

- Are in the IFAP.
- Received a full dose of vaccine at Day 1 and a full dose of vaccine at Day 22 within -3 to +14 days of the expected visit date.
- Received the correct treatment as assigned by randomization.
- Have no other major (important) protocol deviations that may have an impact on immunogenicity assessments. Such deviations will be identified by BARDA via a comprehensive review of all deviations occurring prior to and including the Day 43 visit. This review will be completed prior to the interim database freeze and performing interim analyses. To account for any deviations entered or updated after the interim database freeze, a similar review will be completed prior to the final database lock and performing final analyses.
- Have determinate assay results at the Day 43 visit within -7 to +14 days of the expected visit date.

All immunogenicity analyses will be performed on the IPPP.

6. VALIDATION AND QUALITY CONTROL PROCEDURES

Validation and quality control of datasets, summary tables, data listings, figures, and statistical analyses will be performed in accordance with the Statistical Validation and Quality Control Plan.

7. STUDY PARTICIPANTS

7.1. Treatment Groups

This study will randomize approximately 1380 participants, including 780 participants 18 through 64 years old who will be randomized equally to 1 of 13 treatment groups (A, B, C, D, E, F, G, H, I, J, K, M, and N), and 600 participants ≥65 years old who will be randomized equally to 1 of 10 treatment groups (B, C, E, F, H, I, K, L, N, and O) as listed in Table 2 below.

Table 2: Treatment Groups

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

Separate tables will be created for each antigen type (H5N8 and H5N1) and adjuvant (AS03A Full Dose, AS03A Half Dose, and MF59) combination. Each table will be summarized by age group and treatment group. Tables will include overall summaries (combined age groups), where applicable. The structure of the tables will be outlined in the TLF shells.

7.2. Disposition of Participants

The disposition of all enrolled participants will be summarized in tables and listed. Enrollment is defined as participants who have signed the informed consent form and met all screening eligibility criteria.

The numbers and percentages of participants enrolled, randomized, in each analysis population, completing selected study visits, and terminating early, including reasons for early termination, will be presented. A CONSORT diagram will also be constructed, if needed, to support manuscript preparation. Percentages will be based on the number of participants at each level of summarization and within the specific study group, as applicable. A separate disposition summary using the safety population will be prepared for the CSR.

Participants in each analysis population will be listed. In addition, the reasons for ineligibility at screening, ineligibility at the time of the first vaccination, and ineligibility at the time of the second vaccination will be listed separately.

Length of time on study will be defined for randomized participants as the date of study completion or participant withdrawal **minus** date of Visit 1/Day 1 **plus** 1.

7.3. Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be listed. A summary of descriptive statistics for baseline and demographic characteristics will be reported for each analysis population. Characteristics to be summarized include age at time of randomization (years), age group at time of randomization (18-64 years vs. ≥65 years), race, ethnicity, sex, height (centimeter [cm]), weight (kilogram [kg]), and body mass index (BMI, kg/meter squared [m^2]). Age will be recorded at the time of randomization (during Visit 1/Day 1), and all other characteristics will be recorded at the time of the Screening Visit. These summaries will be presented by treatment group and overall within each antigen type (H5N8 and H5N1) and adjuvant (AS03A Full Dose, AS03A Half Dose, and MF59).

Body weight reported in pounds will be converted to kilograms via body weight in pounds divided by 2.2.

Height reported in inches will be converted to centimeters via height in inches multiplied by 2.54.

BMI will be calculated automatically within the Electronic Data Capture (EDC) system.

7.4. Prior and Concomitant Medications

Medications will be coded according to the World Health Organization (WHO) Drug Dictionary [refer to the Data Management Plan (DMP) for the specific version]. Medications reported will be categorized for analysis as prior or concomitant by comparing the medication start and stop dates with the date of first dose of study vaccine. Prior medications will have a medication start date prior to the first dose of study vaccine date. Concomitant medications will have a medication start date on or after the first dose of study vaccine date or a medication stop date on or after the first dose of study vaccine date. Medications that fit the criteria for both a prior and concomitant medication will be indicated as such in data listings.

The number and percentage of participants receiving prior or concomitant medications will be presented overall and by Anatomical Therapeutic Chemical (ATC) classification level 4 and preferred medication name for the safety population. When reporting the number of participants receiving the medication, a participant will only be counted once if they ever received the medication within the medication class. Percentages will be based on the number of participants in the safety population.

A listing will be created if needed for the CSR.

The following conventions will be used for imputing missing start dates of medications.

- For start dates that are missing the day value with non-missing month and year:
  - If the start year is the same as the year of first date of study vaccine administration, then do the following:
    - If the start month is the same as the month of first date of study vaccine administration, the start date will be imputed as the date of first study vaccine administration.
    - If the start month is the not the same as the month of first date of study vaccine administration, the start date will be imputed as the first day of the non-missing start month.
  - If the start year is not the same as the year of first date of study vaccine administration, then the start day will be imputed as the first day of the non-missing start month.
- For start dates that are missing the day and month values with non-missing year:
  - If the start year is earlier than the year of first date of study vaccine administration, the start month and day will be imputed as July 1.
  - If the start year is the same as the year of first date of study vaccine administration, the start date will be set to the date of Visit 1 (Day 1).
  - If the start year is after the year of first date of study vaccine administration, the start month and start day will be imputed as January 1.
- Completely missing start dates will be imputed as the first date of study vaccine administration.

End dates of medications will not be imputed.

7.5. Prior and Concomitant Immunizations

Immunizations other than the study vaccines will be collected from 90 days prior to Screening through the end of the study on the Immunization Log case report form (CRF). Non-study vaccine immunizations will be categorized for analysis as prior or concomitant by comparing the date of immunization with the date of first dose of study vaccination. Immunization dates prior to the date of first dose of study vaccination will be classified as prior. Immunization dates on or after the first dose of study vaccination date will be classified as concomitant.

The number and percentage of participants receiving prior and concomitant immunizations will be presented overall and by immunization type for the safety population. A participant will only be counted once within a given immunization type. Percentages will be based on the number of participants in the safety population.

A listing will be created if needed for the CSR.

Missing vaccination date parts will be imputed using the same logic as concomitant medication start dates in Section 7.4.

7.6. Medical History

Medical history will be collected at the Screening Visit, per Appendix 1 in the Protocol. A listing of reported medical conditions will be created for the safety population.

The medical history assessment at the Screening Visit also collects whether the participant has received any past pandemic influenza vaccines, and whether the participant has ever received a seasonal influenza vaccine. Past pandemic influenza and seasonal influenza vaccination data will be listed for the safety population.

7.7. Travel and Exposure History

Travel and exposure history will be listed for all participants. Residence outside of the United States for 3 months or more (along with countries of residence and time frames) since 2005, travel outside of the United States (along with countries visited) since 2005, and close contact with wild birds or poultry over the past 3 months preceding screening will be listed.

8. STUDY OPERATIONS

8.1. Protocol Deviations

Protocol deviations are defined in Section 15.3.1 of the protocol. All protocol deviations, including site level protocol deviations, will be listed by site with information such as type of deviation, severity of the deviation (major/important or non-major/non-important), date/day of occurrence, and the reason for the deviation. Protocol deviations will be summarized in tabular format by type of deviation and treatment group for the safety population.

As described in Section 5.3 protocol deviations will be used in determining the composition of the IPPP. Protocol deviations will not be recorded in EDC. Protocol deviations will be recorded via ICON plc's (ICON's) Clinical Trial Management System (CTMS). ICON will be responsible for collection, tracking, and proposing categorization of all protocol deviations. BARDA will review and approve or amend the proposed categorization. The protocol deviation data will be transferred from ICON to Rho on a weekly basis per the Protocol Deviation Data Transfer Agreement.

8.2. Blinding and Randomization

Participants 18 through 64 years old will be randomized equally to 1 of 13 treatment groups (A, B, C, D, E, F, G, H, I, J, K, M, and N), and participants ≥65 years old will be randomized equally to 1 of 10 treatment groups (B, C, E, F, H, I, K, L, N, and O). Randomization will take place according to a fixed schedule using a permuted block design stratified by age group and will be implemented per Section 10.7.1 of the Protocol.

This is a double-blind study. The study staff members who will prepare and/or administer the study vaccine will be unblinded to treatment group assignment. Site investigators, all investigational site staff (except those responsible for preparing/administering the vaccine), and all participants participating in this study will be blinded to treatment group assignment. Laboratory staff performing the safety laboratory assessments and immunogenicity assays will be blinded to treatment group. The unblinded study staff will not be involved with safety evaluations, nor will they perform subsequent assessments or engage in other study activities that could reveal the blind. To preserve the study blind, a minimum number of Rho, ICON, and BARDA personnel will have access to treatment randomization information at the individual participant level. The unblinded Rho study team will include an unblinded statistical team, Rho Client Support Services, and web-based randomization system teams. Additional details pertaining to blinding of ICON and BARDA personnel are available in Section 10.7.2 of the protocol.

8.2.1. Maintaining the Blind Within the Statistical and Programming Team

For all analyses requiring unblinded data from study start through end of study and prior to database unblinding, a blinded programming team consisting of programmers and statisticians will perform all programming tasks (including SDTM datasets, ADaM datasets, and TLFs) and all associated validation tasks using dummy study groups, which will be randomly assigned. After validation of datasets and displays using dummy study groups, an unblinded team of a statistician and programmer will generate, interpret, and report each analysis using actual study groups and will not modify any programs used to perform analyses.

Any necessary modification of dataset or display programs will be communicated from the unblinded team to the blinded team so that the blinded team can modify the coding while being blinded to study groups, after which the unblinded team will rerun analyses using the unblinded data.

Additionally, since the immunogenicity data may be potentially unblinding, a member of the unblinded team will randomly reassign the participant identifiers (IDs) in the input data file so immunogenicity results will be assigned to participants other than those participants to which they correspond. Blinded programming tasks involving immunogenicity data will be performed exclusively using this reassigned file. The immunogenicity file with correct participant ID assignments will only be used for unblinded analyses and, prior to database unblinding, only viewable by the unblinded team.

8.3. Measures of Treatment Compliance

Treatment compliance for dose 1 at Visit 1 (Day 1) and dose 2 at Visit 3 (Day 22) will be listed and summarized by treatment group, within each antigen type and adjuvant, for the safety population. Counts and percentages of participants receiving correct study vaccine, receiving a full dose of study vaccine, or receiving a partial dose of study vaccine will be summarized separately for vaccination dose 1 (Visit 1; Day 1) and vaccination dose 2 (Visit 3; Day 22). Summary tables will also include counts and percentages of participants that did not receive study vaccine at vaccination dose 2 (Visit 3; Day 22), and the reasons the study vaccine was not received, will be summarized. Lastly, for participants that received both doses of study vaccine, counts and percentages of participants that received the correct study vaccine for both doses, received the correct study vaccine for only one dose, and received the incorrect study vaccine for both doses will be summarized. For the summaries of treatment compliance, the denominator will be the number of participants within each treatment group as randomized.

Details of study drug administration will be listed for each participant, including date of preparation/administration, time of preparation completion, volume drawn from antigen vial, volume drawn from adjuvant vial, volume drawn from admixture vial, time of administration, location of administration (left or right deltoid), total volume administered, and reason not administering, if applicable. For participants that terminated vaccine administration, details of vaccination termination will be listed. Reasons for ineligibility to receive study vaccine at Visit 1 (Day 1) and Visit 3 (Day 22) will be listed as described in Section 7.2.

9. EFFICACY EVALUATION

The protocol is designed to assess the safety and immunogenicity of egg-based H5N8 and H5N1 influenza vaccines at different antigen dose levels adjuvanted with AS03A full dose, AS03A half dose (H5N8 only), or MF59, and as such, does not include a formal evaluation of vaccine efficacy.

10. SAFETY EVALUATION

10.1. Overview of Safety Analysis Methods

All safety analyses will be carried out using the safety population defined in Section 5.1 unless otherwise noted. Missing safety information will not be imputed, with the exception of imputation of partial dates for adverse events (AEs) as described in Section 10.2 below.

Summary tables will present AEs summarized by treatment group and overall.

Listings will be prepared for all safety measurements. Unless noted otherwise in a specific section, all listings will be sorted in order of participant ID and time of assessment (e.g., visit, time, and/or event).

10.2. Adverse Events

All reported AEs will, by definition, be considered treatment emergent, as the AE reporting period begins from the time the participant receives the first vaccination and continues until exit from the study.

Solicited and Unsolicited AEs

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

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

All other AEs reported by the participant will be defined as unsolicited AEs. All unsolicited AEs through Day 43 will be recorded. After Day 43, unsolicited AEs will be recorded only if they are defined as SAEs, MAAEs, or pIMDs, as defined below and in protocol Section 12.3.2.

Serious Adverse Events (SAEs)

An AE or Suspected Adverse Reaction (SAR) is considered “serious” if, in the view of either the site investigator or BARDA, it results in any of the following outcomes:

- Death
- Life-threatening adverse event that in the view of the site investigator or BARDA, places the participant at immediate risk of death. This does not, however, include an event that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongs existing hospitalization. Planned hospitalizations will not be reported as SAEs unless categorized as medically important. Emergency room visits and observational admissions of under 24 hours, in themselves, do not qualify as SAEs.

- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly/birth defect.
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience, when based on appropriate medical judgment, they may jeopardize the participant or the participant may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Medically Attended Adverse Events (MAAEs)

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

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

Potentially Immune-Mediated Diseases (pIMDs)

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

For this study, the occurrence of a pIMD is considered to be unexpected and will be reported as a Suspected Unexpected Serious Adverse Reaction (SUSAR) per 21 CFR 312.32.

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

Coding/Grading

All AEs (serious and non-serious) will be classified by system organ class (SOC) and preferred term (PT), according to the Medical Dictionary for Regulatory Activities (refer to the DMP for the specific version). The severity of AEs will be graded as defined by the Food and Drug Administration (FDA) Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (see protocol Section 12.3.3). Relationship of AEs to study vaccine (not related, unlikely related, possibly related, probably related, related) will be assessed by the investigator at each site, based on their opinion.

Imputation of Partial Dates

If the start date of an AE is incomplete or missing, it will be assumed to have occurred on or after the first dose of study vaccine, except if an incomplete date (e.g., month and year) clearly indicates that the event started prior to treatment.

The following conventions will be used for imputing missing start dates.

- For start dates that are missing the day value with non-missing month and year:
  - If the start year is the same as the year of first date of study vaccine administration, then do the following:
    - If the start month is the same as the month of first date of study vaccine administration, the start date will be imputed as the date of first study vaccine administration.
    - If the start month is the not the same as the month of first date of study vaccine administration, the start date will be imputed as the first day of the non-missing start month.
  - If the start year is not the same as the year of first date of study vaccine administration, then the start day will be imputed as the first day of the start month.
- For start dates that are missing the day and month values with non-missing year:
  - If the start year is the same as the year of first date of study vaccine administration, the start date will be set to the date of Visit 1 (Day 1).
  - If the start year is after the year of first date of study vaccine administration, the start month and start day will be imputed as January 1.
- Completely missing start dates will be imputed as the first date of study vaccine administration.

End dates will not be imputed.

Rules for Severity/Relationship

If the severity rating of an AE is missing, the severity will be counted as unknown in the displays.

For summaries/listings of study vaccine-related AEs, the categories of possibly related, probably related, and related will be considered study vaccine-related. If the relationship is missing, it will be counted as study vaccine-related in the displays.

Additionally, when summarizing AEs by severity or relationship, the AE will be categorized according to the highest severity (or relationship) rating for that AE in that participant.

SOC/PT Counting Rules

If a participant experiences the same AE on multiple occasions, the event will be counted once for each occurrence when reporting the number of AEs. When reporting the number of participants experiencing the events, a participant will only be counted once if they experience at least one event within the particular SOC or PT.

AE Summary Tables

The following section describes general summaries of AEs. Planned analyses for the primary and secondary safety endpoints are detailed in Section 10.4, below. For all AE summaries, percentages will be based on the number of participants in the safety population within the treatment group and overall, within each antigen type and adjuvant, as applicable. As described

in Section 5.1, summaries of the safety population for each vaccine dose will be analyzed by treatment group according to the actual treatment received for the applicable vaccine dose, and all other summaries of the safety population will be analyzed according to the actual treatment received for the first vaccine dose. Summary tables will be presented by treatment group and overall within each antigen type (H5N8 and H5N1) and adjuvant (AS03A Full Dose, AS03A Half Dose, and MF59). Summary tables of AEs by SOC and PT and will be sorted by SOC alphabetically and by PT within each SOC by descending overall frequency and then alphabetically.

Separate summaries of solicited local and systemic AEs and unsolicited AEs will be prepared for combined dose 1 and dose 2, dose 1 only, and dose 2 only.

The following rules will apply for including solicited local and systemic AEs in the summaries for combined dose 1 and dose 2, dose 1 only, and dose 2 only:

- Dose 1 only – start dates occurring within 8 days post-vaccination with dose 1, inclusive of the vaccination day (Day 1 through Day 8
- Dose 2 only – start dates occurring within 8 days post-vaccination with dose 2, inclusive of the vaccination day (Day 22 through Day 29)
- Combined dose 1 and dose 2 – start dates occurring within 8 days post-vaccination with either dose 1 or dose 2, inclusive of the vaccination day (Day 1 through Day 8 and Day 22 through Day 29)

The following rules will apply for including unsolicited AEs in the summaries for combined dose 1 and dose 2, dose 1 only, and dose 2 only:

- Dose 1 only – start dates occurring within 22 days following vaccination with dose 1 (Day 1 through Day 22)
- Dose 2 only – start dates occurring within 22 days following vaccination with dose 2 (Day 22 through Day 43)
- Combined dose 1 and dose 2 – start dates occurring after vaccination with dose 1 through the end of the study (Day 203)

Any unsolicited AE that falls on the day of dose 2 administration will be included in the individual dose summaries for dose 2.

Overall summary tables of all AEs will be produced for combined dose 1 and dose 2, as well as individually for dose 1 and dose 2. Overall summary tables will include:

- The number (n) and percentage (%) of participants with at least 1 AE and total number of AEs
- The number (n) and percentage (%) of participants with at least 1 solicited local AE and total number of solicited local AEs
- The number (n) and percentage (%) of participants with at least 1 solicited systemic AE and total number of solicited systemic AEs
- The number (n) and percentage (%) of participants with at least 1 unsolicited AE and total number of unsolicited AEs

- The number (n) and percentage (%) of participants with at least 1 serious AE and total number of serious AEs
- The number (n) and percentage (%) of participants with at least 1 MAAE and total number of MAAEs
- The number (n) and percentage (%) of participants with at least 1 pIMD and total number of pIMDs
- The number (n) and percentage (%) of participants with at least one AE related to study vaccine and total number of AEs related to study vaccine
- The number (n) and percentage (%) of participants with at least one severe AE related to study vaccine
- The number (n) and percentage (%) of participants with at least one AE leading to study vaccine discontinuation and total number of AEs leading to study vaccine discontinuation
- The number (n) and percentage (%) of participants with at least one AE leading to early withdrawal from the study and total number of AEs leading to early withdrawal from the study
- The number (n) and percentage (%) of participants with at least one AE leading to death and total number of AEs leading to death
- The number (n) and percentage (%) of participants with at least one AE by maximum severity grade

The following summary tables by SOC and PT will be produced:

- All AEs by SOC and PT
- AEs leading to early withdrawal from the study by SOC and PT
- All AEs by SOC, PT, and maximum severity grade
- All AEs by SOC, PT, and strongest relationship to study vaccine

Data Listings

Separate listings will be generated for all AEs, SAEs, AEs leading to study vaccine discontinuation, AEs leading to early withdrawal from the study, deaths, MAAEs, and pIMDs for participants in the safety population.

10.3. Deaths, Serious Adverse Events, and Other Significant Adverse Events

Deaths and other serious or significant adverse events will be encompassed by the various adverse event types defined in Section 10.2, and these events will be summarized and listed as described in that section.

A separate listing will be created for all deaths containing the time to death (relative to first date of study vaccine administration) and cause of death.

10.4. Safety Endpoint Analyses

10.4.1. General Considerations

All safety analyses are considered exploratory in nature. As such, no adjustments will be required for multiple comparisons. As no statistical models will be used in the evaluation of the safety endpoints, adjustments for covariates will not be necessary. In addition to the primary analyses for safety endpoints, subgroup analyses will be performed for the safety endpoints by age group (18-64 years old and ≥65 years old). No additional subgroups will be examined.

10.4.2. Analysis of the Primary Safety Endpoints

The primary safety endpoints for this study are as follows:

- Primary Safety Endpoint #1: The percentage of participants who experience any solicited local reactogenicity symptoms occurring within 8 days of each vaccination, inclusive of the vaccination day (Day 1 through Day 8 and Day 22 through Day 29)
- Primary Safety Endpoint #2: The percentage of participants who experience any solicited systemic reactogenicity symptoms occurring within 8 days of each vaccination, inclusive of the vaccination day (Day 1 through Day 8 and Day 22 through Day 29)

Solicited local and systemic reactogenicity symptoms will be collected via participant diaries (paper or ePRO). Diaries are to be completed by participants daily within 8 days of each vaccination, inclusive of the vaccination day (Day 1 through Day 8 and Day 22 through Day 29). The site investigator or his/her designee reviews the information collected via the participant diaries at each follow-up visit post-vaccination [Visit 2 (Day 8) and Visit 4 (Day 29)] to assess whether reported symptoms meet any AE criteria based on FDA's standard toxicity grading scales (see protocol Section 12.1.6).

As defined in protocol Section 12.3.2, due to expectedness of mild symptoms, the primary safety endpoints will only count solicited symptoms that meet AE criteria. Additionally, events will be included in the primary safety endpoints only if they occur within 8 days of each vaccination, inclusive of vaccination day (Day 1 through Day 8 and Day 22 through Day 29).

Summaries for primary safety endpoint #1 will be presented by SOC and PT and will include the number and percentage of participants experiencing solicited local reactogenicity symptoms, corresponding 95% exact (Clopper-Pearson) CI, and the total number of solicited local reactogenicity symptoms. Primary safety endpoint #2 will be summarized in a similar manner.

All summaries of the primary safety endpoints will be presented by treatment group and overall within each antigen type (H5N8 and H5N1) and adjuvant (AS03A Full Dose, AS03A Half Dose, and MF59).

Separate summaries will be prepared for combined dose 1 and dose 2, dose 1 only, and dose 2 only. The following rules will apply for including events in the primary safety endpoint summaries:

- Dose 1 only – start dates occurring within 8 days post-vaccination with dose 1, inclusive of the vaccination day (Day 1 through Day 8)

- Dose 2 only – start dates occurring within 8 days post-vaccination with dose 2, inclusive of the vaccination day (Day 22 through Day 29)
- Combined dose 1 and dose 2 – start dates occurring within 8 days post-vaccination with either dose 1 or dose 2, inclusive of the vaccination day (Day 1 through Day 8 and Day 22 through Day 29)

Using the same method as described above, the primary safety endpoints will be summarized by maximum severity and by strongest relationship to study vaccine.

10.4.3. Analysis of the Secondary Safety Endpoints

The secondary safety endpoints are listed below.

- Secondary Safety Endpoint #1: The percentage of participants who experience any unsolicited treatment-emergent AE within 22 days of each vaccination, inclusive of the vaccination day (Day 1 through Day 22 and Day 22 through Day 43).
- Secondary Safety Endpoint #2: The percentage of participants who experience any treatment-emergent SAE through Day 203.
- Secondary Safety Endpoint #3: The percentage of participants who experience any treatment-emergent MAAE through Day 203.
- Secondary Safety Endpoint #4: The percentage of participants who experience any treatment-emergent pIMD through Day 203.

As explained in Section 10.2, all AEs recorded in this study are, by definition, treatment-emergent AEs.

All four secondary safety endpoints will be summarized using the similar methods as the primary safety endpoints (described in Section 10.4.2). The endpoints will be presented by SOC and PT and summarized for the time periods listed in the bullets above.

For secondary safety endpoint #1, separate summaries will be prepared for combined dose 1 and dose 2, dose 1 only, and dose 2 only. Secondary safety endpoint #1 will also be summarized by maximum severity, strongest relationship to study vaccine, and earliest day of onset after study drug administration (≤8 days vs. >8 days).

For secondary safety endpoint #1, the following rules will apply for including events in the independent summaries for dose 1 only and dose 2 only:

- Dose 1 only – start dates occurring in the period of Day 1 through Day 22
- Dose 2 only – start dates occurring in the period of Day 22 through Day 43

Based on the rules above, if the start date of an unsolicited AE falls on Day 22, the event will be included in individual summaries for dose 2.

For secondary safety endpoint #1, the following rule will apply for including events in the combined dose 1 and dose 2 summaries:

- Combined dose 1 and dose 2 – start dates occurring in the periods of Day 1 through Day 43

For summaries by earliest day of onset after study drug administration (≤8 days vs. >8 days), day of onset relative to the most recent study vaccine administration will be derived. If a participant experiences the same unsolicited AE multiple times, the event with the closest start date to study vaccine administration will be counted.

10.5. Clinical Laboratory Evaluation

Clinical laboratory measurements of serum chemistry and hematology will be performed at a central laboratory. Results will be converted to standardized units where possible. For numeric laboratory results, descriptive statistics of laboratory values and the change from baseline of laboratory values will be presented. For categorical laboratory results, the number and percentage of participants reporting each result will be presented. Summaries of clinical laboratory results will be presented for the safety population by treatment group and overall within each antigen type (H5N8 and H5N1) and adjuvant (AS03A Full Dose, AS03A Half Dose, and MF59). Baseline will be defined as described in Section 4.

If two or more evaluations occur in the same visit window, the evaluation closest to the target visit day will be selected for inclusion in the analysis. If multiple evaluations are equally close to the target visit day, then the latest evaluation will be selected for inclusion in the analysis.

Laboratory data may also be plotted to show patterns over time. For each test with a numeric result, quantile plots with treatment group means (or medians) as well as 25th and 75th percentiles plotted over time will be created. Tests with qualitative results (such as “present” or “positive”) will not be plotted.

Clinical laboratory results will receive a toxicity grade according to protocol Appendix 2. Results which meet AE reporting criteria will be presented with the AE displays.

All clinical laboratory data will be presented in one or more listings.

10.6. Vital Signs, Physical Findings, and Other Observations Related to Safety

10.6.1. Vital Signs

Vital signs will be collected by the local centers. Measurements include blood pressure (systolic and diastolic) (millimeters of mercury [mmHg]), pulse rate (beats/minute), respiratory rate (breaths/minute), and oral temperature (°F). Descriptive statistics of vital signs and the change from baseline of vital signs will be presented for the safety population by treatment group and overall, within each antigen type (H5N8 and H5N1) and adjuvant (AS03A Full Dose, AS03A Half Dose, and MF59). Baseline will be defined as described in Section 4.

If two or more evaluations occur in the same visit window, the evaluation closest to the target visit day will be selected for inclusion in the analysis. If multiple evaluations are equally close to the target visit day, then the latest evaluation will be selected for inclusion in the analysis.

Vital signs will receive a toxicity grade according to protocol Appendix 2. Results which meet AE reporting criteria will be presented with the AE displays.

All vital sign data will be presented in one or more listings.

10.6.2. Physical Examinations

Full physical examination results will be recorded at screening, and a targeted physical exam will be performed at subsequent visits, per Appendix 1 in the protocol. Potential body systems assessed include skin, HEENT (head, eyes, ears, nose, and throat), neck, thyroid, lungs, cardiovascular system, abdomen, lymph nodes, musculoskeletal system/extremities, and neurological.

Physical examination results of normal, abnormal, and not done will be displayed by body system for each visit and summarized as frequencies and percentages of participants by treatment group and overall, within each antigen type (H5N8 and H5N1) and adjuvant (AS03A Full Dose, AS03A Half Dose, and MF59), for the safety population. Percentages will be based on the number of participants in the safety population with available data at each visit in each treatment group and overall, within each antigen type, as applicable.

If two or more evaluations occur in the same visit window, the evaluation closest to the target visit day will be selected for inclusion in the analysis. If multiple evaluations are equally close to the target visit day, then the latest evaluation will be selected for inclusion in the analysis.

All physical exam data will be presented in one or more listings.

10.6.3. Other Safety Measures

10.6.3.1. Pregnancy Assessments

An onsite urine pregnancy test will be performed for all women of childbearing potential at the Screening Visit and within 24 hours prior to each vaccination at Visit 1 (Day 1) and Visit 3 (Day 22). Additionally, a urine pregnancy test should be performed at any time during study participation if pregnancy is suspected. Date, time, and results of each pregnancy assessment will be listed for all female participants of childbearing potential. In the case of one or more pregnancies occurring during study participation, a data listing will be prepared to display applicable information, including date reported, method of pregnancy confirmation, delivery date (if applicable), pregnancy termination status and week (if applicable), and any problems or congenital abnormalities present for each birth.

10.6.3.2. Vaccination Site Examination

Examination of the vaccination site will be performed per protocol Appendix 1 and will include assessment of erythema/redness, induration/swelling, and pain. Frequencies and percentages of participants experiencing these conditions will be summarized by visit and treatment group within each antigen type (H5N8 and H5N1) and adjuvant (AS03A Full Dose, AS03A Half Dose, and MF59) for the safety population. Percentages will be based on the number of participants in the safety population with available data at each assessment in each treatment group, within each antigen type and adjuvant combination, as applicable. Descriptive summaries of the largest diameter (cm) of erythema/redness and induration/swelling will be presented as well.

Vaccination site examination information will also be listed for each participant, dose, and visit. Information included will be vaccine administration date, time of vaccine administration date, date of examination, time of examination, days since vaccination, and all information summarized in vaccination site examination tables described in the paragraph above.

10.6.3.3. Diary Card Measurements

Participant-reported diary card measurements of injection site redness and injection site induration/swelling will be listed for each participant in the safety population.

11. IMMUNOGENICITY EVALUATION

11.1. Overview of Analysis Methods

All immunogenicity summaries will be carried out using the IPPP and repeated using the IFAP as a secondary analysis, as described in Section 5, unless otherwise stated. Due to the exploratory nature of the study objectives, no formal hypothesis testing is planned. Missing immunogenicity data will not be imputed; all descriptive summaries will be based upon all available data. Since no statistical models will be used for the evaluation of the primary and secondary immunogenicity endpoints, adjustments for covariates will not be necessary. All immunogenicity comparisons of treatment groups are considered exploratory in nature, and as such, no adjustments will be required for multiple comparisons. All analyses of immunogenicity endpoints will be summarized by age group and treatment group, within each antigen type and adjuvant combination. No overall analyses (combined age groups) will be performed for immunogenicity endpoints.

Primary and secondary immunogenicity endpoints will be derived based on serum HAI antibody titers and serum MN antibody titers to A/Astrakhan (H5N8), and serum HAI antibody titers and serum MN antibody titers to A/bar-headed goose (H5N1). Antibody titers will be measured by a central laboratory using the immunogenicity profile samples collected per Appendix 1 in the protocol. Antibody titers that are undetectable or have a value that is less than the lower limit of quantitation (LLOQ) will be imputed as LLOQ divided by 2 (or half the LLOQ). Antibody titers that are above the upper limit of quantification (ULOQ) will be imputed as ULOQ.

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

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

11.1.1. Assessment Time Windows

Allowable visit windows for immunogenicity profile collection are provided in Appendix 1 of the protocol. For immunogenicity analyses performed on the IPPP, the immunogenicity data must fall within the following windows to be included in the analyses:

- Screening immunogenicity serum sample collection prior to vaccine at Day 1
- Day 22 immunogenicity serum sample collection within -3 to +14 days of the expected visit date
- Day 43 immunogenicity serum sample collection within -7 to +14 days of the expected visit date

- Day 203 immunogenicity serum sample collection within -14 to +14 days of the expected visit date

For immunogenicity analyses performed on the IFAP, immunogenicity data from visits that occur outside of the scheduled window will not be excluded from analyses, provided the IFAP criteria are otherwise met.

Immunogenicity data is not expected to be collected at unscheduled or early termination visits. Data from unscheduled visits will be included in listings but will generally not be included in tabular or graphical summaries. The one exception is if the unscheduled visit occurs during the allowable visit window of a missed visit; any available immunogenicity data from the unscheduled visit will be included in the summary of the missed visit data.

11.1.2. Timing of Analyses

The analyses generated for the Day 43 interim analysis (see Section 13) will support a Day 43 interim analysis CSR. All analyses generated for the final analysis at the end of study, following final database lock and unblinding, will support a final analysis CSR. Details of the plan to maintain the blind when generating the TLFs and CSR for the Day 43 interim analysis are included in Section 13.

11.2. Primary Immunogenicity Endpoint

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

11.2.1. Computation of Primary Immunogenicity Endpoint

The primary immunogenicity endpoint will be computed using the results for serum HAI antibody titers to A/Astrakhan (H5N8) from samples collected at Day 43 based on the definition of seroprotection to serum HAI antibody titers specified in Section 11.1.

11.2.2. Analysis of Primary Immunogenicity Endpoint

The primary immunogenicity endpoint will be summarized as the number of participants with non-missing data at the visit, number and percentage of participants achieving seroprotection at Day 43 based on serum HAI antibody titers to A/Astrakhan (H5N8), and the corresponding 95% exact (Clopper-Pearson) CI. In addition, the seroprotection rate and corresponding 95% CI will be displayed graphically by age group and treatment group on Day 43.

The analyses of the primary immunogenicity endpoint will be performed using the IPPP and repeated as a secondary analysis using the IFAP.

As a supportive analysis, the specified success criteria for HAI antibody titers are that the 95% lower bound CI for the seroprotection rate are greater than 70% for participants aged 18-64 years old, and greater than 60% for participants aged 65 years and older.

The following hypothesis will be tested within each treatment group for participants aged 18-64 years old:

1. H_o: Seroprotection rate for HAI antibody titers at Day 43 is less than or equal to 70%.
   H_a: Seroprotection rate for HAI antibody titers at Day 43 is greater than 70%.

The following hypothesis will be tested within each treatment group for participants aged 65 years and older:

1. H_o: Seroprotection rate for HAI antibody titers at Day 43 is less than or equal to 60%.
   H_a: Seroprotection rate for HAI antibody titers at Day 43 is greater than 60%.

These p-values will be descriptive and no statistical significance will be declared for p-values < 0.05.

11.3. Secondary Immunogenicity Endpoints

The secondary immunogenicity endpoints are listed below:

- The percentage of participants achieving seroprotection at Day 43 based on serum HAI antibody titers (≥1:40) to A/bar-headed goose (H5N1).
- Serum HAI antibody titers to A/Astrakhan (H5N8) at Screening and Days 22, 43, and 203.
- Serum HAI antibody titers to A/bar-headed goose (H5N1) at Screening and Days 22, 43, and 203.
- The percentage of participants achieving seroprotection at Days 22 and 203 based on serum HAI antibody titers (≥1:40) to A/Astrakhan (H5N8).
- The percentage of participants achieving seroprotection at Days 22 and 203 based on serum HAI antibody titers (≥1:40) to A/bar-headed goose (H5N1).
- The percentage of participants achieving seroconversion at Days 22, 43, and 203 based on serum HAI antibody titers to A/Astrakhan (H5N8).
- The percentage of participants achieving seroconversion at Days 22, 43, and 203 based on serum HAI antibody titers to A/bar-headed goose (H5N1).
- Serum MN antibody titers to A/Astrakhan (H5N8) at Screening and Days 22, 43, and 203.
- Serum MN antibody titers to A/bar-headed goose (H5N1) at Screening and Days 22, 43, and 203.
- The percentage of participants achieving seroconversion at Days 22, 43, and 203 based on serum MN antibody titers A/Astrakhan (H5N8).
- The percentage of participants achieving seroconversion at Days 22, 43, and 203 based on serum MN antibody titers A/bar-headed goose (H5N1).

11.3.1. Computation of Secondary Immunogenicity Endpoints

Seroprotection and seroconversion endpoints will be computed based on the definitions of seroprotection and seroconversion outlined in Section 11.1. For the continuous serum HAI and MN antibody titer immunogenicity endpoints, a $\log_2$ transformation will be applied to the antibody levels for statistical analysis.

For secondary immunogenicity endpoints involving Days 22 and 203, immunogenicity data may be excluded from the IPPP analyses based on a review by BARDA of major protocol deviations

that may have an impact on immunogenicity assessments at these timepoints. This review will be completed prior to the final database lock and performing final analyses.

11.3.2. Analysis of Secondary Immunogenicity Endpoints

The seroprotection and seroconversion endpoints will be summarized as described in Section 11.2.2 for the primary immunogenicity endpoint. Summaries of seroprotection and seroconversion endpoints will be displayed by visit for each immunogenicity profile timepoint [i.e. Screening (seroprotection only), Visit 3 (Day 22), Visit 5 (Day 43), Visit 6 (Day 203)]. Analyses of seroconversion endpoints will only be performed using the IPPP.

The supportive analyses described in Section 11.2.2 for the primary immunogenicity endpoint will also be performed for the following secondary immunogenicity endpoint: seroprotection at Day 43 based on serum HAI antibody titers (≥1:40) to A/bar-headed goose (H5N1).

As additional supportive analyses, the specified success criteria for HAI antibody titers and MN antibody titers are that the 95% lower bound CI for the seroconversion rate are greater than 40% for participants aged 18-64 years old, and greater than 30% for participants aged 65 years and older.

The following hypotheses will be tested within each treatment group for participants aged 18-64 years old:

1. H_o: Seroconversion rate for HAI antibody titers at Day 43 is less than or equal to 40%.
   H_a: Seroconversion rate for HAI antibody titers at Day 43 is greater than 40%.
2. H_o: Seroconversion rate for MN antibody titers at Day 43 is less than or equal to 40%.
   H_a: Seroconversion rate for MN antibody titers at Day 43 is greater than 40%.

The following hypotheses will be tested within each treatment group for participants 65 years and older:

1. H_o: Seroconversion rate for HAI antibody titers at Day 43 is less than or equal to 30%.
   H_a: Seroconversion rate for HAI antibody titers at Day 43 is greater than 30%.
2. H_o: Seroconversion rate for MN antibody titers at Day 43 is less than or equal to 30%.
   H_a: Seroconversion rate for MN antibody titers at Day 43 is greater than 30%.

The p-values for these hypothesis tests will be descriptive and no statistical significance will be declared for p-values < 0.05.

Each of the continuous serum HAI and MN antibody titer immunogenicity endpoints will be summarized with the following descriptive statistics:

- number of participants with non-missing data at the visit
- geometric mean titer (GMT) and corresponding standard deviation
- asymptotic 95% CI based on the t distribution about the GMT
- minimum and maximum values
- median and 1st and 3rd quartile values

Summaries will be displayed by visit for each immunogenicity profile timepoint noted in the endpoint. The GMT data summarized in tables will be plotted on the $\log_2$ scale with corresponding 95% CIs by age group and treatment group within each antigen type and adjuvant; visits (i.e. expected study day) will be displayed on the horizontal axis. The reverse cumulative distribution of GMT at each immunogenicity profile timepoint noted in the endpoint will also be plotted by age group and treatment group, within each antigen type and adjuvant, with percent on the vertical axis and antibody levels on the horizontal axis.

A data listing of serum antibody titers will be prepared, which will include seroprotection (for HAI antibody titers only) and seroconversion (for HAI and MN antibody titers separately) at each applicable visit.

11.4. Exploratory Analyses of Immunogenicity Endpoints

For seroprotection rates (HAI antibody titers only) and geometric mean titers (for HAI and MN antibody titers separately) at Day 43, the following exploratory comparisons will be performed on the IPPP for descriptive purposes only. No statistical significance can be declared based on p-values < 0.05. Summaries will be presented by age group and treatment group within each antigen type and adjuvant. The exploratory comparisons between the treatment groups within each antibody/adjuvant pairing are listed below:

- Within the H5N8/AS03A Full dose pairing:
  - 3.75 µg (Group A) vs. 7.5 µg (Group B)
  - 3.75 µg (Group A) vs. 15 µg (Group C)
  - 7.5 µg (Group B) vs. 15 µg (Group C)
- Within the H5N8/AS03A Half dose pairing:
  - 3.75 µg (Group D) vs. 7.5 µg (Group E)
  - 3.75 µg (Group D) vs. 15 µg (Group F)
  - 7.5 µg (Group E) vs. 15 µg (Group F)
- Within the H5N8/MF59 pairing:
  - 3.75 µg (Group G) vs. 7.5 µg (Group H)
  - 3.75 µg (Group G) vs. 15 µg (Group I)
  - 7.5 µg (Group H) vs. 15 µg (Group I)
- Within the H5N1/AS03A Full dose pairing:
  - 3.75 µg (Group J) vs. 7.5 µg (Group K)
  - 3.75 µg (Group J) vs. 15 µg (Group L)
  - 7.5 µg (Group K) vs. 15 µg (Group L)
- Within the H5N1/MF59 pairing:
  - 3.75 µg (Group M) vs. 7.5 µg (Group N)

  - 3.75 µg (Group M) vs. 15 µg (Group O)
  - 7.5 µg (Group N) vs. 15 µg (Group O)

The exploratory comparisons between the adjuvants within each antibody/antigen dose level are listed below:

- Within the H5N8/AS03A pairing:
  - 3.75 µg: AS03A Full Dose (Group A) vs AS03A Half Dose (Group D)
  - 7.5 µg: AS03A Full Dose (Group B) vs AS03A Half Dose (Group E)
  - 15 µg: AS03A Full Dose (Group C) vs AS03A Half Dose (Group F)
- Within the H5N1/AS03A pairing:
  - 3.75 µg: AS03A Full Dose (Group J) vs AS03A Half Dose (Group M)
  - 7.5 µg: AS03A Full Dose (Group K) vs AS03A Half Dose (Group N)
  - 15 µg: AS03A Full Dose (Group L) vs AS03A Half Dose (Group O)

The null hypothesis for each of the comparisons is that there is no difference between the 2 groups. Each alternative hypothesis is that there is a difference between the 2 groups.

Seroprotection rate will be compared between groups using a two-sided Fisher's exact test. Risk differences will be displayed with corresponding 95% exact unconditional CIs (based on the Santner and Snell method) and p-values.

Serum HAI and MN antibody titers (log-transformed) will be compared between groups using a t-test. Geometric mean ratios will be displayed with corresponding 95% t-type CIs and p-values.

Serum HAI antibody titers against A/Astrakhan (H5N8) and against A/bar-headed goose (H5N1) at Day 43 will be plotted against each other as a scatterplot with a regression line on the $\log_2$ scale. The Pearson correlation coefficient will be presented with the corresponding p-value. This analysis will be performed on the IPPP. Serum MN antibody titers against A/Astrakhan (H5N8) and against A/bar-headed goose (H5N1) at Day 43 will be plotted in a similar manner. This analysis will be repeated on the subset of participants who were in close contact with wild birds or poultry over the 3 months preceding screening.

Additionally, for HAI and MN antibody titers, separately, geometric mean titers against A/bar-headed goose (H5N1) will be compared to geometric mean titers against A/Astrakhan (H5N8) at each immunogenicity profile timepoint by age group and treatment group within each antigen type and adjuvant combination. Summaries will include geometric mean ratio and corresponding 95% t-type CIs and p-values. The comparisons will be performed on the IPPP for descriptive purposes only and no statistical significance will be declared.

11.5. Exploratory Immunogenicity Endpoints

No other endpoints are pre-specified.

11.6. Other Endpoints

No other endpoints are pre-specified.

12. OTHER ANALYSES

No other analyses are planned.

13. INTERIM ANALYSES AND DATA MONITORING

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

13.1. Interim Analysis of Safety and Immunogenicity Data

An interim analysis will be performed based on available cumulative immunogenicity data through Day 43 for all participants and all available safety data for all participants. At the time of the interim analysis, the study database (all available immunogenicity data through Day 43 and all available safety data) will be monitored per the Clinical Monitoring Plan and cleaned per the DMP.

The unblinded Day 43 interim analysis will be compiled by an unblinded statistical team, and the unblinded interim analysis TLFs will support the unblinded Day 43 interim analysis CSR. As the unblinded Day 43 interim analysis CSR will contain participant-data listings, the unblinded Day 43 interim analysis CSR will only be compiled and reviewed by unblinded team members in order to maintain the blind for those outside of the unblinded team until database lock of all data through the end of study. In addition to the unblinded Day 43 interim analysis CSR, a subset of top-line tables, aggregated at the treatment group level and therefore maintaining participant-level blinding, will be provided to the BARDA blinded team members.

Available primary, secondary immunogenicity, and secondary safety #1 endpoints through Day 43 and all available secondary safety #2, #3, and #4 endpoints will be analyzed as specified in Section 10.4.2 and Section 10.4.3 for safety endpoints and Section 11.2.2 and Section 11.3.2 for immunogenicity endpoints. The interim analysis will also include summaries and/or listings of participant disposition, demographic and baseline characteristics, prior and concomitant medications and immunizations, medical history, protocol deviations, treatment compliance, and other safety measures as specified in this SAP.

The unblinded team will generate all necessary displays, and the unblinded statistical team will be responsible for providing results to the unblinded medical writing team and unblinded BARDA team members, as well as assisting with development of the unblinded interim analysis CSR. Information regarding unblinded roles and personnel, protections/processes in place to restrict unblinded data, and a communication plan for dissemination of the unblinded interim analysis results are detailed in the Blinding/Unblinding Plan.

No decisions regarding the status of the study will be made as a result of the interim analysis.

14. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

Protocol Section 13.1.2.4 specifies that data from the Day 43 interim analysis will be aggregated at the group level, maintaining participant-level blinding for those outside of the unblinded team until database lock of all data through the end of the study. However, Section 13.1 of this SAP clarifies that the unblinded Day 43 interim analysis CSR will contain participant-data listings therefore it will be compiled and reviewed by unblinded team members only. A separate delivery of top-line tables, aggregated at the group-level and therefore maintaining participant-level blinding, will be provided to BARDA blinded team members.

Protocol Section 13.1.2.4 specifies that an interim analysis will be performed based on available cumulative immunogenicity and safety data through Day 43 for all participants. Due to the necessity to include all available safety events including those that occur after Day 43 in the interim analysis, Section 13.1 of this SAP states all available safety data will be included in the interim analysis.

Protocol Section 13.1.2.1.3 outlines the criteria for participants' inclusion in the IPPP. The IPPP criteria in Section 5.3 of this SAP were modified to specify the allowable timeframe for receiving the second dose of vaccine (-3 to +14 days of the expected visit date) and collection of the Day 43 immunogenicity sample (-7 to +14 days of the expected visit date).

Protocol Section 13.1.2.1 specifies that all immunogenicity analyses will be performed on the IFAP and IPPP. However, Sections 5, 11.1, and 11.2 of this SAP clarify that the immunogenicity analysis conducted on the IPPP will be primary and immunogenicity analyses may be repeated on the IFAP as a secondary analysis.

The secondary safety endpoints #2, #3, and #4 will not be summarized by vaccination (i.e., Dose 1 or Dose 2), onset days following each vaccination, maximum severity, and relatedness to the study vaccine, as specified in Protocol Section 13.1.2.3. Additionally, neither the primary nor secondary safety endpoints will be summarized by duration.

15. REFERENCES

None.

16. APPENDIX

16.1. Schedule of Events

The schedule of events is contained in Appendix 1 of the protocol.

17. ATTACHMENTS

TLF shells will be prepared as a separate document to this SAP.