Statistical Analysis Plan

Study ID: 219833

Official Title of Study: A Phase I/II observer-blind, randomized, multi-center trial to evaluate the safety and immunogenicity of different formulations of monovalent Influenza A/Astrakhan /3212/2020 like (H5N8) virus vaccine with AS03 adjuvant system (referred to as Q-Pan H5N8), given as a two-dose series to adults 18 to 64 years of age and 65 years of age and older

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STATISTICAL ANALYSIS PLAN

219833 (FLU Q-PAN H5N8=AS03-001)

A Phase I/II observer-blind, randomized, multi-center trial to evaluate the safety and immunogenicity of different formulations of monovalent Influenza A/Astrakhan /3212/2020 like (H5N8) virus vaccine with AS03 adjuvant system (referred to as Q-Pan H5N8), given as a two-dose series to adults 18 to 64 years of age and 65 years of age and older

AUTHOR: PPD

VERSION NUMBER AND DATE: V5.0, 19AUG2024

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V5.0 (Dated 19AUG2024) for Protocol 219833.

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	15MAY2023	PPD	Not Applicable – First Version
2.0	20JUL2023		Reference and updates due to protocol amendment 1.0. Extended collection of MAEs to Visit 6/EOS (6 months post dose 2). Updated Study Schema Figure A to be in line with the figure presented in the protocol amendment 1.0. Updated Interim Section to include details provided in the protocol. Amendment to Demographic and Other Baseline Characteristics section to include table for Per Protocol set. Amendment to General Considerations section to include detail on analysis being provided for age groups, to be in line with Protocol. Details added to Safety section 16.1.1 to include an additional solicited events table.
3.0	11JAN2024	PPD	Section 2.3 Statistical Hypothesis, 2.5 Sample size determination, Section 4.2 Interim Analysis, Section 6.4 Window Convention (table B and C), and Section 7.4 updated according to changes in protocol amendment 3.0.SPR confidence intervals amended from 98.75% to 95% throughout document. Added detail to Section 16 Safety outcomes, to note shell on shift Laboratory toxicity table. Added detail regarding imputing completely missing dates on

			Appendix 2.
4.0	22MAY2024	PPD	Section 16.2 Laboratory Assessment Events – outputs are to display all increases in laboratory toxicity grading from baseline to after each vaccination, opposed to only an increase to Grade 2 or higher. Wording “to Grade 2 [moderate] or higher” removed.
5.0	19AUG2024		Section 15 - As per request from FDA, addition of sensitivity analysis to be performed on the primary endpoints, to evaluate the immunogenicity in subjects who had Visit 3 and 5 performed within the study windows [14-28 days], as specified in Protocol version 1 amendment 2.

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LIST OF ABBREVIATIONS

Abbreviation	Term
ANCOVA	Analysis of covariance
CBER	Center for Biologics Evaluation and Research
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence interval
COVID-19	Coronavirus Disease 2019
DMC	Data monitoring committee
DS	Diary set
eCRF	Electronic case report form
ENR	Enrolled set
EOS	End of study
ES	Exposed set
GCP	Good clinical practice
GMFR	Geometric mean fold rise from visit 1
GMT	Geometric mean titers
H5N8	Monovalent Influenza A/Astrakhan/3212/2020-like virus

HA	Hemagglutinin adjuvanted
HI	Hemagglutination inhibition
LL	Lower limit
MAE	Medically attended adverse events
MedDRA	Medical dictionary for regulatory activities
MN	Microneutralization
PD	Protocol deviations
PDMP	Protocol deviations management plan
PI	Principal investigator
pIMD	Potential immune-mediated disease
PPS	Per protocol set
PT	Preferred term
Q1	1st quartile
Q3	3rd quartile
RCC	Reverse cumulative distribution
SCR	Screened set
SD	Standard deviation
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Seroconversion
SCR	Seroconversion rate

SOC	System organ class
SP	Seroprotection
SPR	Seroprotection rate
SRT	Safety review team
TFL	Tables, figures and listings
ULOQ	Upper limit of quantification
VR	Vaccine response
VRR	Vaccine response rate
WHODD	World Health Organization Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) describes the rules and conventions to be used in the presentation and analysis of immunogenicity and safety analyses for Protocol 219833 (H5N8). It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This SAP is based on the protocol amendment 3.0 dated 16 February 2024.

2. STUDY OBJECTIVES AND ESTIMANDS

2.1. Primary Objective

Objectives	**Endpoints (Population Summary)**
Co-Primary	
Immunogenicity: To evaluate whether the monovalent influenza A/Astrakhan/3212/2020-like (H5N8) virus vaccine containing 3.75 µg, or 7.5 µg of HA with $AS03_A$ or $AS03_B$ elicits a HI response to the vaccine -homologous virus that meets or exceeds the US Food and Drug Administration, Center for Biologics Evaluation and Research immunogenicity criteria at the Day 43 visit.	Humoral immune response in terms of: • Vaccine-homologous HI titers at Day 43 (i.e., GMT). • Vaccine-homologous HI titers increase at Day 43 compared to pre-vaccination (i.e., GMFR). • SP defined as titer $\geq$ 1:40 at Day 43 (percentage of participants meeting SP criteria).
Safety: To evaluate the safety and reactogenicity of the different vaccine formulations through the Day 43 visit and SAEs and pIMDs through Day 43 and also 6 months post dose 2.	• Occurrence of each solicited administration site event during a 7-day follow-up period (i.e., day of vaccination and 6 subsequent days) after each vaccination (percentage of participants with occurrence). • Occurrence of each solicited systemic event during a 7-day follow-up (i.e., day of vaccination and 6 subsequent days) after each vaccination (percentage of participants with occurrence). • Occurrence of toxicity grade increase in either hematology or biochemistry laboratory tests 7

Objectives	Endpoints (Population Summary)
	days after each vaccination (percentage of participants with change from baseline). • Occurrence of unsolicited AEs for 21 days (i.e., day of vaccination and 20 subsequent days) after each vaccination (percentage of participants with occurrence). • Occurrence of MAEs for 21 days (i.e., day of vaccination and 20 subsequent days) after each vaccination and also through 6 months post dose 2 (percentage of participants with occurrence). • Occurrence of SAEs until Day 43 and also 6 months post dose 2 (percentage of participants with occurrence). • Occurrence of pIMDs until Day 43 and also 6 months post dose 2 (percentage of participants with occurrence).

Abbreviations: AE=adverse event; GMFR=geometric mean fold rise; GMT=geometric mean titer; HA=hemagglutinin; HI=hemagglutination inhibition; H5N8=monovalent influenza A/Astrakhan/3212/2020-like; MAE=medically attended adverse event; pIMD=potential immune-mediated disease; SAE=serious adverse event; SP=seroprotection; US=United States.

2.2. Secondary Objectives

Objectives	Endpoints (Population Summary)
Secondary	
To describe the vaccine-homologous (H5N8) HI profile in all study groups at Days 1, 22, 43, and 6 months post dose 2.	Vaccine-homologous (H5N8) HI titers for each study group: • Vaccine-homologous HI titers at Day 1, 22, and 6 months post dose 2 (GMT). • Vaccine-homologous HI titers increase from pre-vaccination at Day 22 and 6 months post dose 2 (GMFR). • SP defined as titer ≥1:40 at Day 1, 22, and 6 months post dose 2 (percentage of participants meeting SP criteria).

Objectives	Endpoints (Population Summary)
	• HI SC defined as titer ≥1:40 for participants with pre-vaccination titer below 1:10 or a ≥4-fold increase from pre-vaccination titer for participants with pre-vaccination titer ≥1:10 at Day 22, Day 43 and 6 months post dose 2 (percentage of participants meeting SC criteria).
To describe the vaccine-homologous (H5N8) MN titers in a subset* of participants at Days 1, 22, and 43, and 6 months post dose 2	Vaccine-homologous (H5N8) MN titers for a subset of participants: • MN titers at Days 1, 22, and 43 and 6 months post dose 2 (GMT). • Seropositivity rates defined as percentage of participants with reciprocal titer above LLOQ at Days 1, 22, 43, and 6 months post dose 2 (percentage of seropositive participants). • MN VR defined as titer ≥4× LLOQ for participants with pre-vaccination titer below LLOQ or a ≥4 -fold increase from pre-vaccination titer for participants with pre-vaccination titer ≥LLOQ at Days 22, 43, and 6 months post dose 2 (percentage of participants meeting VR criteria).

Abbreviations: AE=adverse event; GMFR=geometric mean fold rise; GMT=geometric mean titer; HI=hemagglutination inhibition; H5N8=monovalent influenza A/Astrakhan/3212/2020-like; LLOQ=lower limit of quantitation; MN=microneutralization; SC=seroconversion; SP=seroprotection; SPR=seroprotection rate; VR=vaccine response.

* Subset for Microneutralization testing will be performed on 50% of the participants, randomly selected and equally distributed across the different age subgroups.

2.3. Statistical Hypotheses

The null hypotheses for vaccine-homologous HI titer at Day 43 (in 18 to 64 years of age or in 65 years of age or above) are:

For 18 to 64 years of age: $H0_1$: seroprotection rate (SPR) < 70%
For 65 years of age or above: $H0_2$: SPR < 60%

Null hypotheses will be assessed according to a hierarchical order of study groups as given below.

1. 7.5 mcg antigen + AS03A
2. 7.5 mcg antigen + AS03B
3. 3.75 mcg antigen + AS03A
4. 3.75 mcg antigen + AS03B

No multiplicity adjustment is required as the hypothesis for each study group will be tested if the success criteria will be met for the previous group in the hierarchy. Accordingly, a nominal type I error of 2.5% will be used for each dose group and the objective will be met for one dose group if all 2 null hypotheses are rejected simultaneously.

Criteria for success to be met simultaneously for a study group:

- The lower limit (LL) of the 95% confidence interval (CI) for the SPR meets or exceeds 70% for adults of 18 to 64 years of age.
- The LL of the 95% confidence interval (CI) for the SPR meets or exceeds 60% for adults ≥65 years of age.

2.4. Estimands

The primary, and secondary estimands to support regulatory decisions are described in the following table and are applicable for young adults (18-64 years of age) and older adults(65 years of age or older) separately:

	Study Intervention	Analysis set	Variable (or endpoint)	Intercurrent events (ICEs)		Population level summary
				Description	Handling strategy	
Primary	The study intervention will be defined by the first dose administered	PPS	Titers for vaccine-homologous HI titers at day 43	1. Study vaccination not administered as per protocol 2. Prohibited medication or intercurrent medical condition prior to Visit 4 (Day 43) 3. Blood sample taken out of window at Day 43 See section 5.6 and 9.2 for further details.	Participants will be excluded from the analysis at Day 43 See section 5.6 and 9.2 for further details on handling the intercurrent events and protocol deviations	GMTs with 2-sided 95% CI for vaccine-homologous HI titers at Day 43 for each study intervention group using ANCOVA. The ANCOVA model includes dose group effect as a fixed effect and log-transformed titer pre-dose 1 (Day 1) as a covariable.
Primary	The study intervention will be defined by the first dose administered	PPS	GMFR for vaccine-homologous HI titers at day 43	Refer to first primary endpoint	Refer to first primary endpoint	GMFR, with ANCOVA derived 95% CIs, for vaccine-homologous HI titers at Day 43 for each study intervention group. The ANCOVA model includes dose group effect

	Study Intervention	Analysis set	Variable (or endpoint)	Intercurrent events (ICEs)		Population level summary
				Description	Handling strategy	
						as a fixed effect and log-transformed titer pre-dose 1 (Day 1) as a covariable.
Primary	The study intervention will be defined by the first dose administered	PPS	HI SP at day 43, defined as vaccine-homologous H5N8 HI titer ≥ 1:40	Refer to first primary endpoint	Refer to first primary endpoint	SPR, defined as percentage of participants meeting SP definition, will be reported with Clopper-Pearson exact 2-sided 95% CIs at Day 43 for each study intervention group.
Primary	The study intervention will be defined by the first dose administered	DS	Solicited administration site events within 7 days after each vaccine administration	1. Paper diary not completed on each day	1. Missing data won't be imputed. Compliance to paper diary will be captured	Percentage and exact 95% CIs of participants with solicited administration site events within 7 days after each vaccine administration.
Primary	The study intervention will be defined by the first dose administered	DS	Solicited systemic event within 7 days after each vaccine administration	1. Paper diary not completed on each day	1. Missing data won't be imputed. Compliance to paper diary will be captured	Percentage and exact 95% CIs of participants with solicited systemic events within 7 days after each vaccine administration.
Primary	The study intervention will be defined by the first dose administered	ES	Each toxicity grade change from baseline in hematology or biochemistry laboratory tests 7 days after each vaccine administration	1.Permanently discontinued from study due to any reasons prior to Day 7	1.Missing data won't be imputed. Summaries will present the actual data	Percentage and exact 95% CIs of participants with toxicity grade change from baseline for hematology or biochemistry laboratory

	Study Intervention	Analysis set	Variable (or endpoint)	Intercurrent events (ICEs)		Population level summary
				Description	Handling strategy	
						tests 7 days after each vaccine administration
Primary	The study intervention will be defined by the first dose administered	ES	Each unsolicited adverse event within 21 days after each vaccine administration	1. Permanently discontinued from study due to any reasons prior to Day 21	1. Missing data won't be imputed. Summaries will present the actual data	Percentage and exact 95% CIs of participants with unsolicited adverse events within 21 days after each vaccine administration.
Primary	The study intervention will be defined by the first dose administered	ES	Each medically attended adverse event (MAE) within 21 days after each vaccine administration and also through 6 months post dose 2	1. Permanently discontinued from study due to any reasons prior to Day 21	1. Missing data won't be imputed. Summaries will present the actual data	Percentage and exact 95% CIs of participants with MAEs within 21 days after each vaccine administration.
Primary	The study intervention will be defined by the first dose administered	ES	Each serious adverse event (SAE) by Day 43 and within 6 months post dose 2	1. Permanently discontinued from study due to any reasons prior to end of study	1. Missing data won't be imputed. Summaries will present the actual data	Percentage and exact 95% CIs of participants with SAEs by Day 43 and within 6 months post dose 2
Primary	The study intervention will be defined by the first dose administered	ES	Each Potential Immune-Mediated Disease (pIMD) event by Day 43 and within 6 months post dose 2	1. Permanently discontinued from study due to any reasons prior to end of study	1. Missing data won't be imputed. Summaries will present the actual data	Percentage and exact 95% CIs of participants with pIMDs by Day 43 and within 6 months post dose 2.
Secondary	The study intervention will be defined by the first dose administered	PPS	Geometric Mean Titers (GMTs) for vaccine-homologous HI titers at Day 1, 22 and 6 months	Refer to first primary endpoint, in addition 1. Prohibited medication or intercurrent medical	Refer to first primary endpoint 1. If these exclusion conditions are met prior	GMTs with 2-sided 95% CI for vaccine-homologous HI titers at Day 1, 22, and 6 months

	Study Intervention	Analysis set	Variable (or endpoint)	Intercurrent events (ICEs)		Population level summary
				Description	Handling strategy	
			post dose 2	condition prior to Visit 3 (Day 22) or 6 months post dose 2 blood sampling 2. Vaccine or blood sample taken out of window	to Visit 3 (Day 22), then the participant would be excluded from immunogenicity analysis at Day 22 and at 6 months post dose 2. 2. If these exclusion conditions are met prior to 6 months post dose 2, then participant excluded from the immunogenicity analysis at 6 months post dose 2.	post dose 2. The CI will be computed from an ANCOVA model which includes dose group effect as a fixed effect and log-transformed titer pre-dose 1 (Day 1) as a covariable. For Day 1, t-student CI will be used.
Secondary	The study intervention will be defined by the first dose administered	PPS	GMFR for vaccine-homologous HI titers at Day 22 and 6 months post dose 2	Refer to first primary endpoint. in addition. 1. Prohibited medication or intercurrent medical condition prior to Visit 3 (Day 22) or 6 months post dose 2blood sampling 2. Vaccine or blood sample taken out of window	Refer to first primary endpoint in addition. 1. If these exclusion conditions are met prior to Visit 3 (Day 22), then the participant would be excluded from immunogenicity analysis at Day 22 and at 6 months post dose 2. 2. If these exclusion	GMFR, with ANCOVA derived 95% CIs, for vaccine-homologous HI titers, at Day 22, and 6 months post dose 2 for each study intervention group. The ANCOVA model includes dose group effect as a fixed effect and log-transformed titer pre-dose 1 (Day 1) as a covariable.

	Study Intervention	Analysis set	Variable (or endpoint)	Intercurrent events (ICEs)		Population level summary
				Description	Handling strategy	
					conditions are met prior to 6 months post dose 2, then participant excluded from the immunogenicity analysis at 6 months post dose 2.	
Secondary	The study intervention will be defined by the first dose administered	PPS	HI SP, defined as vaccine-homologous H5N8 HI titer ≥ 1:40 at Day 1, 22, and 6 months post dose 2	Refer to first primary endpoint in addition. 1. Prohibited medication or intercurrent medical condition prior to Visit 3 (Day 22) or 6 months post dose 2 blood sampling 2. Vaccine or blood sample taken out of window	1.If these exclusion conditions are met prior to Visit 3 (Day 22), then the participant would be excluded from immunogenicity analysis at Day 22 and at 6 months post dose 2. 2. If these exclusion conditions are met prior to 6 months post dose 2, then participant excluded from the immunogenicity analysis at 6 months post dose 2.	SPR, defined as percentage of participants meeting SP definition, will be reported with Clopper-Pearson exact 2-sided 95% CIs at Day 1, 22, and 6 months post dose 2 for each study intervention group.

	Study Intervention	Analysis set	Variable (or endpoint)	Intercurrent events (ICEs)		Population level summary
				Description	Handling strategy	
					3. Missing data won't be imputed. Summaries will present the actual data.	
Secondary	The study intervention will be defined by the first dose administered	PPS	HI SC, defined as vaccine-homologous H5N8 HI titer ≥ 1:40 in the serum of participants with visit 1 titer below 1:10 or as a ≥ 4-fold rise in post-vaccination HI titer with pre-vaccination titer ≥ 1:10 at Day 22, Day 43 and 6 months post dose 2	Refer to first primary endpoint in addition. 1. Prohibited medication or intercurrent medical condition prior to Visit 3 (Day 22) or 6 months post dose 2 blood sampling 2. Vaccine or blood sample taken out of window	1. If these exclusion conditions are met prior to Visit 3 (Day 22), then the participant would be excluded from immunogenicity analysis at Day 22, Day 43 and at 6 months post dose 2. 2. If these exclusion conditions are met prior to Visit 5 (Day 43), then participant excluded from the immunogenicity analysis at Day 43 and 6 months post dose 2. 3. If these exclusion conditions are met prior to 6 months post dose 2, then participant	SCR, defined as percentage of participants meeting SC definition, will be reported with Clopper-Pearson exact 2-sided 95% CIs at Day 22, and 6 months post dose 2 for each study intervention group.

	Study Intervention	Analysis set	Variable (or endpoint)	Intercurrent events (ICEs)		Population level summary
				Description	Handling strategy	
					excluded from the immunogenicity analysis at 6 months post dose 2. 4. Missing data won't be imputed. Summaries will present the actual data.	
Secondary	The study intervention will be defined by the first dose administered	PPS (in subset of adult participant with MN titers)	GMTs for vaccine-homologous MN neutralization titers at Day 1, 22, 43, and 6 months post dose 2	Refer to first primary endpoint in addition. 1. Prohibited medication or intercurrent medical condition prior to Visit 3 (Day 22) or 6 months post dose 2 blood sampling 2. Vaccine or blood sample taken out of window	1. If these exclusion conditions are met prior to Visit 3 (Day 22), then the participant would be excluded from immunogenicity analysis at Day 22 and 6 months post dose 2. 2.If these exclusion conditions are met prior to Visit 5 (Day 43), then the participant would be excluded from analysis at Day 43 and at 6 months post dose 2. 3. If these exclusion conditions are met prior	GMTs with 2-sided 95% CI for vaccine-homologous MN neutralization titers at Day 1, 22, 43, and 6 months post dose 2. The CI will be computed from an ANCOVA model which includes dose group effect as a fixed effect and log-transformed titer pre-dose 1 (Day 1) as a covariable. For Day 1, t-student CI will be used.

	Study Intervention	Analysis set	Variable (or endpoint)	Intercurrent events (ICEs)		Population level summary
				Description	Handling strategy	
					to 6 months post dose 2, then participant excluded from the immunogenicity analysis at 6 months post dose 2. 4. Missing data won't be imputed. Summaries will present the actual data.	
Secondary	The study intervention will be defined by the first dose administered	PPS (in subset of adult participant with MN titers)	Seropositivity rates, defined as percentage of participants with reciprocal titer above LLOQ, for vaccine-homologous MN neutralization titers at Day 1, 22, 43, and 6 months post dose 2	Refer to first primary endpoint, in addition. 1. Prohibited medication or intercurrent medical condition prior to Visit 3 (Day 22) or 6 months post dose 2 blood sampling 2. Vaccine or blood sample taken out of window	1. If these exclusion conditions are met prior to Visit 3 (Day 22), then the participant would be excluded from immunogenicity analysis at Day 22 and 6 months post dose 2. 2.If these exclusion conditions are met prior to Visit 5 (Day 43), then the participant would be excluded from analysis at Day 43 and at 6 months post dose 2.	Percentage of seropositive participants, with Clopper-Pearson exact 2-sided 95% CI, for vaccine-homologous MN neutralization titers at Day 1, 22, 43, and 6 months post dose 2.

	Study Intervention	Analysis set	Variable (or endpoint)	Intercurrent events (ICEs)		Population level summary
				Description	Handling strategy	
					3. If these exclusion conditions are met prior to 6 months post dose 2, then participant excluded from the immunogenicity analysis at 6 months post dose 2. 4. Missing data won't be imputed. Summaries will present the actual data. .	
Secondary	The study intervention will be defined by the first dose administered	PPS (in subset of adult participant with MN titers)	Vaccine response (VR) defined as titer ≥ 4 x lower limit of quantification (LLOQ) for participants with pre-vaccination titer below LLOQ or a ≥ 4-fold increase from pre-vaccination titer for participants with pre-vaccination titer ≥ LLOQ for vaccine-homologous MN	Refer to first primary endpoint, in addition. 1. Prohibited medication or intercurrent medical condition prior to Visit 3 (Day 22) or 6 months post dose 2 blood sampling 2. Vaccine or blood sample taken out of window	1.If these exclusion conditions are met prior to Visit 3 (Day 22), then the participant would be excluded from immunogenicity analysis at Day 22 and 6 months post dose 2. 2.If these exclusion conditions are met prior to Visit 5 (Day 43), then the participant would be	Vaccine response rate (VRR), defined as percentage of participants meeting definition for VR, with Clopper-Pearson exact 2-sided 95% CI for vaccine-homologous MN neutralization titers at Day 22, 43, and 6 months post dose 2.

	Study Intervention	Analysis set	Variable (or endpoint)	Intercurrent events (ICEs)		Population level summary
				Description	Handling strategy	
			neutralization titers at Day 22, 43, and 6 months post dose 2		excluded from analysis at Day 43 and at 6 months post dose 2. 3. If these exclusion conditions are met prior to 6 months post dose 2, then participant excluded from the immunogenicity analysis at 6 months post dose 2. 4.. Missing data won't be imputed. Summaries will present the actual data.	

2.5. Sample size determination

A total of 520 participants are planned to be enrolled, with 65 participants per age subgroup in each of the 4 dose groups.
A non-evaluable rate of 23% and 30% in 18 to 64 years of age and ≥65 years of age groups, respectively yield an approximate sample size of 95 evaluable participants per dose group (i.e., 50 participants between 18 to 64 years of age and 45 participants above 65 years of age in each dose group), giving 77.8% overall power to fulfill the 2 SPR immunogenicity criteria in the first group that is 7.5 mcg antigen + AS03A (detailed further in Section 3.1). This assumes that the SPR is truly 20% higher than the critical value (namely 90% for participants 18 to 64 years of age and 80% for participants ≥ 65 years of age, respectively).

The statistical power in 7.5 mcg antigen + AS03A group will be 91.4% if the SPR is assumed as 85% in ≥65 years of age.

3. STUDY DESIGN

3.1. General Description

This is a phase I/II, observer-blind, randomized, age stratified, multi-center study in healthy adults of ≥ 18 years of age with four parallel groups, which will be conducted in the US. Participants will be randomly assigned to 4 study groups at Visit 1 (Day 1).
Each of these 4 groups will be stratified by age group to create 8 subgroups of equal size in each dose group: 18 to 64 years of age (approximately 50% of participants enrolled) and ≥ 65 years of age (approximately 50% of participants enrolled).
All analyses will be provided separately for each age group.
Each participant will receive 2 intramuscular dose of study vaccine 21 days apart. Each participant will participate for 6 months after receipt of the final dose administered.

- 375_B group: Study intervention administration of 3.75 µg and AS03B on Visit 1 (Day 1) and 21 days later
- 375_A group: Study intervention administration of 3.75 µg and AS03A on Visit 1 (Day 1) and 21 days later
- 750_B group: Study intervention administration of 7.50 µg and AS03B on Visit 1 (Day 1) and 21 days later
- 750_A group: Study intervention administration of 7.50 µg and AS03A on Visit 1 (Day 1) and 21 days

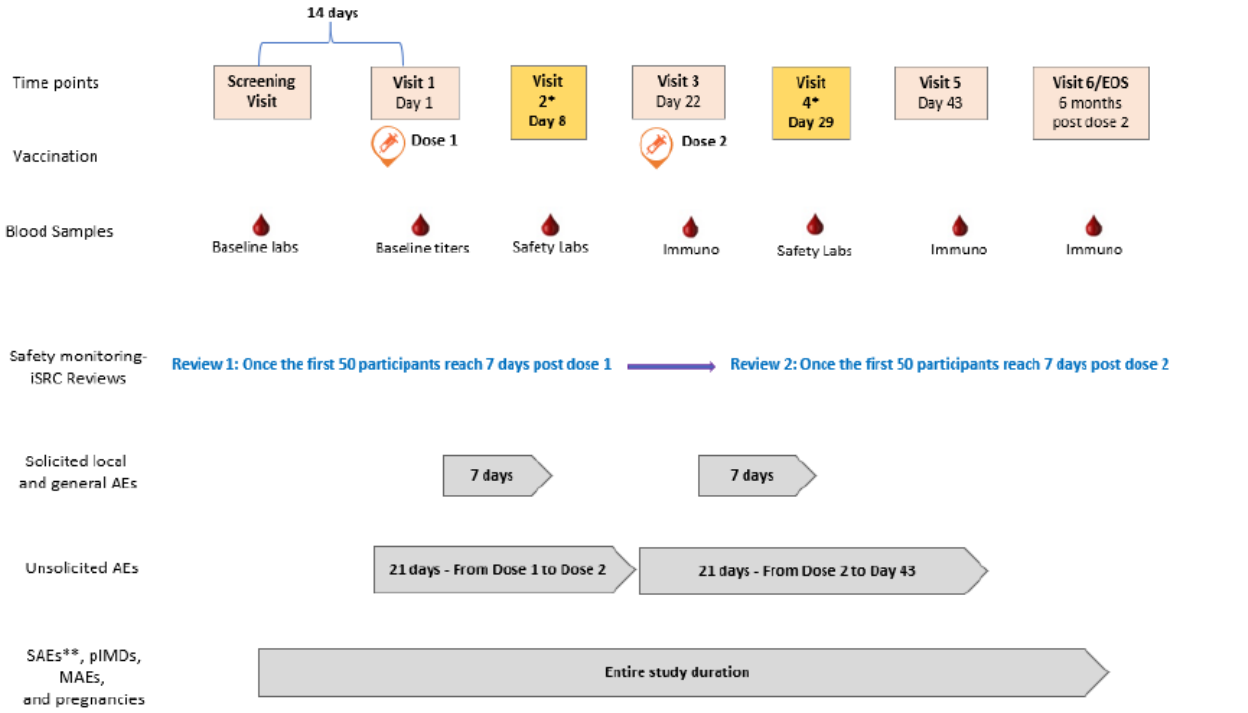
later

Table A Study Groups

Study groups	Number of participants	Age (years of age)	Study interventions
375_B	65	18 to 64	3.75 µg and AS03B
375_B	65	≥ 65	3.75 µg and AS03B
375_A	65	18 to 64	3.75 µg and AS03A
375_A	65	≥ 65	3.75 µg and AS03A
750_B	65	18 to 64	7.50 µg and AS03B
750_B	65	≥ 65	7.50 µg and AS03B
750_A	65	18 to 64	7.50 µg and AS03A
750_A	65	≥ 65	7.50 µg and AS03A

All the participants will have screening laboratory tests to determine eligibility for the study. The first 50% of enrolled participants in each age and dose group will be required to have onsite visits for safety laboratory tests 7 days after each vaccination (i.e., Visit 2 and Visit 4). All other participants will have a remote visit (e.g., telephone call, video call, email, or text communication) with the site.

Figure A: Study Schema



*** Visit 2 and Visit 4→ First 50% participants in each dose and age group will be site visit for safety lab draw; the remaining 50% will have Remote Visit**
**** Only SAEs related to study participation will be collected between Screening and Visit 1.**

There could be additional unscheduled or ad-hoc visit for repeat safety lab draws if indicated between Visits 2 and 3; Visits 4 and 5

Abbreviations: AE=adverse event; EOS=end of study; immuno=immunogenicity blood draw; iSRC=internal safety review committee; MAE=medically attended adverse event; pIMD=potential immune-mediated disease; SAE=serious adverse event.

3.2. Schedule of Events

Schedule of events can be found in Section 1.3 of the protocol. Refer also to Table B.

3.3. Changes to Analysis from Protocol

No changes.

4. PLANNED ANALYSES

The following analyses will be performed for this study:

- Analyses for Safety Review Team (SRT) and Internal Safety Review Committee (iSRC) review
- Interim Safety Analysis at Day 43
- Interim Immunogenicity Analysis at Day 43
- Final Analysis

All planned analyses identified in this SAP will be performed by IQVIA Biostatistics following Sponsor Authorization of this SAP, Database Lock and Sponsor Authorization of Analysis Sets.

Unblinded summaries for the iSRC will be performed by a separate IQVIA team.

4.1. SRT and iSRC Reviews

SRT Review

The SRT is responsible for ongoing safety monitoring and will monitor cumulative, blinded safety data (including serious and non-serious AEs).

iSRC Review

The iSRC is a review body internal to GSK but external to the vaccine project who will review unblinded data at the planned safety reviews of the first 50 participants upon reaching 7 days post dose 1 and also upon reaching 7 days post dose 2.
Enrollment will be capped to 20 participants per day until the iSRC reviews have been completed. Following iSRC recommendation, the enrollment will be opened with no limitations.
Further details on the iSRC will be included in a separate iSRC charter

4.2. Interim Analysis

The interim analysis, including reactogenicity, safety and immunogenicity data, is planned when data collected through to, and including, the Day 43 visit, is available for all participants.

4.2.1. Interim Safety Analysis at Day 43

An analysis will be performed on data collected through the Day 43 visit. Elements will include:

- Analyses of cleaned solicited administration site events and solicited systemic events data collected during a 7-day follow-up period (i.e., day of vaccination and 6 subsequent days) after each vaccination.
- Analyses of unsolicited AEs reported up to the Day 43 visit (i.e., day of vaccination and 20 subsequent days after each vaccine) and cleaned in so far as is possible, will be carried out.
- Analyses of SAEs, pIMDs, MAEs, pregnancies, and withdrawals due to AEs, collected up to the Day 43 visit, will be carried out.
- No study report will be prepared. Access to individual treatment codes will be restricted to the designated statisticians in charge of the analysis. No individual listings or data with the participants' identifying information will be disseminated. Listings of final data will be provided with the EOS report.

4.2.2. Interim Immunogenicity Analysis at Day 43

An analysis will be performed on data collected through the Day 43 visit. Elements will include:

- Analyses of cleaned immunogenicity data, for analysis of vaccine-homologous HI antibody titers and MN titers, collected through the Day 43 visit will be conducted.
- Results will be presented in a Day 43 statistical report. Access to individual treatment codes will be restricted to the designated statisticians in charge of the analysis. No individual listings or data with the participants' identifying information will be disseminated. Listings of final data will be provided with the EOS report.

All analyses will be performed on data that has been cleaned and locked. The possibility of post-analysis changes to data evaluated at Day 43 exists, since data collection and data entry may continue through 6 months post dose 2. All final data will be presented in the listings provided at 6 months post dose 2.

4.3. Final Analysis

The final analysis includes all data obtained until 6 months post-last dose (end of study [EOS]) and includes safety summaries along with immunogenicity endpoints summaries.

This SAP is focused / limited to planned interim and final analyses. Outputs required for the interim analyses will be flagged in the tables, figures and listings (TFL) mock shells document.

5. ANALYSIS SETS

Agreement and authorization of participant data included/excluded from each analysis set and rules for excluding data requiring knowledge of unblinded data will be obtained prior to the unblinding of the study.

5.1. Process for Analysis Set Assignment

- Prior to database lock, a transfer of raw data from the electronic Case Report Form (eCRF) will occur, and participants will be assigned to analysis sets in accordance with the definitions in this SAP and the available data at that time. However, protocol deviations will be monitored continuously throughout the study.
- Listings for participants excluded from each final analysis set and reasons for exclusion will be prepared for sponsor review ahead of database lock in order to allow appropriate related data queries to be issued.
- A Data Review meeting will be held to confirm analysis set assignment, along with protocol deviations review (see protocol deviations management plan [PDMP], to include details of which protocol deviations (PDs) lead to exclusion from per protocol analyses), for each participant and any changes will be recorded. Changes will be implemented, and an updated analysis set assignment will be approved by the sponsor.
- Sponsor authorization of the analysis sets will be necessary prior to database lock. Once approved, analysis sets will be finalized, and the database will be locked.
- After database lock, the final analysis sets will be derived using the final study data, i.e., clinical database (eCRF), external vendor data (immunogenicity results) and protocol deviations log.

5.2. Screened Set [SCR]

All participants who were screened for eligibility.

5.3. Enrolled Set [ENR]

All participants who were randomized, received study intervention or had immunogenicity blood sample. For analyses and displays based on ENR, participants will not be presented by study group.

5.4. Exposed Set [ES]

Participants who received a study intervention. For analyses and displays based on ES, participants will be classified according to study intervention administered at dose 1 (i.e., study intervention actually received).

5.5. Diary Set [DS]

Participants who received a study intervention and provided information (at least one AE for at least one day) on any solicited AE. For analyses and displays based on DS, participants will be classified according to study intervention administered at dose 1 (i.e., study intervention actually received). Participants to have at least one day of complete diary data to be included in DS.

5.6. Per Protocol Set [PPS]

All eligible participants who received the 2 doses of study intervention as per-protocol, had Day 1 and post dose anti-HI immunogenicity results on Day 43 as per blood draw interval at Day 43.
In addition, participant data at a specific blood draw visit will be excluded from the PPS when:

- Results from a blood sample deviated from blood draw intervals (refer to protocol Table 1)
- Results from a blood sample occurred after intercurrent conditions that may interfere with immunogenicity (i.e., malignancy, immunosuppressive or immunodeficient conditions) or after a prohibited concomitant medication/vaccination.

Critical data missed or eliminated from PPS among participants in the ES will be classified as important protocol deviations.

6. GENERAL CONSIDERATIONS

Data will be summarized descriptively (frequency and percentage for categorical data and mean, standard deviation [SD] and range for continuous data, unless specified otherwise). In summary tables for categorical data for which categories are defined on the eCRF, all categories will be presented as specified, even if the participants count within that category is zero. All analyses will be provided separately for each age groups 18 to 64 years of age and for 65 years of age or above.
Unless otherwise specified, all data collected during the trial will be presented in listings for the ENR.

6.1. Reference Start Date and Study Day

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events. It will appear in every listing where an assessment date or event date appears.

In general, the reference start date is defined as the day of the first dose of each study vaccination, which is Day 1 for all participants.

- If the date of the event is on or after the reference date, then:
  - Study Day = (date of event – reference date) + 1.
- If the date of the event is prior to the reference date, then:
  - Study Day = (date of event – reference date).

For some domains such as AE start, medication start day the reference date is the date of last study vaccination, and this is complemented by the number of previous study vaccinations.
In the situation where the event date is partial or missing, refer to APPENDIX 2.

6.2. Baseline

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to the first study intervention (including unscheduled assessments) and will be referenced as pre-vaccination. In the case where the last non-missing measurement and the reference start date coincide, and time is not collected, that measurement will be considered pre-vaccination. If time is not collected, Day 1 (Visit 1) assessments are assumed to be taken prior to first dose and used as pre-vaccination values.

6.3. Retests, Unscheduled Visits and Early Termination Data

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Repeat safety laboratory assessments at ad-hoc visits will not be included in by-visit summaries. The safety laboratory assessments at ad-hoc visits will be presented in listings.

6.4. Windowing Conventions

Allowed time window for each visit will be performed as mentioned in "Schedule of Activities", section 1.3 of protocol. Intervals between study visits are included in Table B and window conventions are included in

Table C. In case vaccination or lab sample planned at a visit was made on another day, the same interval window will be used for the actual vaccination/lab sample date.
In protocol amendment 3.0 version the visit interval windows have been updated for Visit 1 → Visit 3 and Visit 3 → Visit 5, from 14-28 days to 14-35 days. The window visits have been extended due to the large number of participants whose Visit 3 or Visit 5 was out of window due to the enrolment hold. The Window convention in table C are updated accordingly.

Table B: Intervals between Study Visits

Interval	Planned visit interval	Allowed interval range
Screening → Visit 1	Up to 14 days	14 days
Visit 1 → Visit 2	7 days	7-9 days
Visit 1 → Visit 3	21 days	14-35 days
Visit 3 → Visit 4	7 days	7-9 days
Visit 3 → Visit 5	21 days	14-35 days
Visit 3 → Visit 6	180 days post dose 2	165-195 days

Table C: Window convention

Assigned Study Day	Visit label as per protocol	Visit assigned
Day 1	Visit 1	Visit 1 (Day 1)
Day 8	Visit 2	Visit 2 (Day 8-10)
Day 22	Visit 3	Visit 3 (Day 15-36)
Day 29	Visit 4	Visit 4 (Day 22-45)
Day 43	Visit 5	Visit 5 (Day 29-71)

6.5. Statistical Tests

The default significant level will be (5%); confidence intervals (CIs) will be 95%, unless otherwise specified in the description of the analyses.
CI for proportion will be based on exact Clopper-Pearson CI [Section 18].
The group adjusted geometric mean titers (GMT) ratio will be based on a back transformation of group contrast in an Analysis of Covariance (ANCOVA) model applied to the logarithm-transformed titers.

6.6. Common Calculations

GMT:

Distributions of antibodies are generally skewed to the right (Section 18). Therefore, prior to any statistical analysis that assumes normally distributed observations, titers will be log10-transformed. GMTs and their 95% CI are computed by exponentiating (base 10) the least squares mean and 95% CI of the log10 titers.

The GMT at visit i will be calculated using the following formula:

$$10^{\frac{\sum_{i=1}^{n} log10\,(t_i)}{n}}$$

GMT calculations are performed by taking the inverse logarithm of the mean of the log10 titer transformations. Likewise the GMFR at visit i and associated CI will be calculated from the same formula with t_i replaced by t_i / t_1 Non-quantifiable titers will be converted as described in Table D for the purpose of GMT / GMFR calculation. Numerical serology results will be derived from the content of IS.ISORRES in the SDTM dataset. For all the assays available for the study, assay derivation rules are included in Table D.

Table D: Assay Derivation Rules

IS.ISORRES	Derived value
"NEG", "-", or "(-)"	LLOQ/2
"POS", "+", or "(+)"	Value
"< value" and value is ≤ LLOQ	LLOQ/2
"> value" and value is < LLOQ	LLOQ/2
"> value" and value is ≥ LLOQ	Value
"value" and value is < LLOQ	LLOQ/2
"value" and value is ≥ ULOQ	ULOQ
"value" and value is > ULOQ	ULOQ
All other cases	missing

Note: The Reverse Cumulative Distribution (RCD) generated will not use the upper limit of quantification (ULOQ) values but the exact value if the exact value is greater than ULOQ.

6.7. Software Version

All analyses will be conducted using SAS version 9.4 or above.

7. STATISTICAL CONSIDERATIONS

7.1. Adjustments for Covariates and Factors to be Included in Analyses

The following factors and covariates will be used in the ANCOVA analyses: study intervention group (375_B, 375_A, 750_B, 750_A) as a fixed effect and the $\log_{10}$-transformed titer pre-dose 1 (Day 1) as a covariate. For details, refer to 15.1 and 15.2.

7.2. Multicenter Studies

This study will be conducted by multiple investigators at multiple centers within the United States (US). The participants will be randomized to one of the 4 groups (refer to 25) which will be performed in a 1:1:1:1 ratio prior to intervention to provide approximately 130 enrolled participants per study intervention group. No subgroup or adjustment is planned for study effect.

7.3. Missing Data

Missing data (missing, incomplete or partial dates, AE measurement [including missing AE severity and relationship], prior and concomitant medications and death date) will be handled as per APPENDIX 2 of this SAP.

Missing immunogenicity data will not be imputed. Titers below LLOQ will be replaced by LLOQ/2 for the purpose of GMT computation. Titers above the ULOQ will be replaced by the ULOQ.

7.4. Multiple Comparisons/ Multiplicity

There are 2 primary endpoints to be accounted for in this study. Success will be achieved if the 2 criteria are met simultaneously:

- LL of the 95% CI for the SPR ≥ 70% for adults 18 to 64 years of age, AND
- LL of the 95% CI for the SPR ≥ 60% for adults ≥ 65 years of age.

No multiplicity adjustment is required as the hypothesis for each study group will be tested if the success criteria will be met for the previous group in the hierarchy. Accordingly, a nominal type I error of 2.5% will be used for each dose group and the objective will be met for one dose group if all 2 null hypotheses are rejected simultaneously.

7.5. Examination of Subgroups

All endpoints will be produced separately for each age group: 18 to 64 years of age and ≥ 65 years of age.

8. OUTPUT PRESENTATIONS

APPENDIX 1 shows conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be provided by IQVIA Biostatistics. Statistical output numbering will follow 'ICH E3 Structure and Content of Clinical Study Reports'.

9. DISPOSITION AND WITHDRAWALS

9.1. Disposition

Participant disposition will be summarized for the enrolled set across groups and for ES for each study group and overall. Specifically, the number of participants enrolled but not exposed will be summarized with reason for no exposure. The number of exposed participants will be summarized to provide the number who completed study vaccinations, who discontinued vaccinations, who completed the study, who discontinued from the study with the reason for discontinuation.

9.2. Protocol Deviations

Protocol deviations (PDs) will be collected in a PD log, as detailed in the PDMP. All PDs will be assessed as either important or non-important. PDs will be reviewed by the sponsor, and their status confirmed by the time that all data are cleaned for the Interim and Final Analyses. A summary table presenting the number and percentage of participants with important PDs (i.e., those PDs associated to elimination from PPS and DS), and the number and percentage of participants excluded from the PPS and DS analyses respectively will be presented for participants in the ES by study intervention and overall. A listing of all PDs including an indicator of those important, excluded from the ES, PPS and DS will be provided for the ENR.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the ES and PP sets. The following demographic and other baseline characteristics will be reported for this study:

- Age (years) – at the time of first study intervention
- Age category (18-64 and ≥ 65 years of age)
- Sex
- Race (as per Clinical Data Interchange Standards Consortium [CDISC] categories)
- Ethnicity
- Center
- Occupation

Descriptive statistics (mean, median, standard deviation, and range) will be presented for continuous variables and frequency counts and percentages for categorical variables. A listing for demographic and other baseline characteristics will be provided for the ENR.

No statistical testing will be carried out for demographic or other baseline characteristics.

Pregnancy test results pre-vaccination will be presented in a listing, for the ENR.

11. GENERAL MEDICAL / VACCINATION HISTORY AND EXAMINATIONS

Medical / Vaccination History information will be summarized for the ES.

- Medical History will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 25.1 or higher.
- Data captured on the "Medical History" page of the eCRF will be presented by System Organ Class (SOC), High Level Terms (HLT) and Preferred Term (PT). Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History section of the eCRF, not the adverse events (AE) section. However, if medical occurrences are considered by the investigator to be related to study conduct, then this would be reported as an AE.

A listing of medical / vaccination history data will be provided.

12. PRIOR, CONCOMITANT AND CO-ADMINISTERED VACCINATIONS

Prior, concomitant and co-administered vaccination will be coded with the current version of the World Health Organization Drug Dictionary (WHODD), summarized and listed, for the ES.

- Prior vaccinations are vaccinations given to participants prior to the dosing of first study intervention.
- Concomitant vaccinations are defined as any vaccine that the participant is receiving on or after the day of the first administration of study intervention.

13. MEDICATIONS

Medications will be presented for the ES. The number and percentage of participants and doses using concomitant medication during the 21-day follow-up period (i.e., on the day of each vaccination and 20 subsequent days) will be summarized by study intervention group for each study intervention administration and overall will be summarized. Medications will be summarized using WHO ATC level 3 categories.
See APPENDIX 2 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior or concomitant, the medication will be classified by the worst case; i.e., concomitant.

Further details are in Section 6.8 of the Protocol. Concomitant medications that are taken within 21-days follow-up period post each vaccination will be presented in table summaries and in listings for all medications. Medications will be listed for the ES.

14. STUDY MEDICATION EXPOSURE

Exposure to study intervention will be presented for the ES.

15. IMMUNOGENICITY OUTCOMES

The primary analysis will be based on the PPS for analysis of immunogenicity. If, in any study intervention group, the percentage of vaccinated participants with serological results excluded from the PPS at one of the post intervention time points is 5% or more, a second analysis based on the ES will be performed to complement the PPS analysis.
A sensitivity analysis will also be performed on the primary endpoints, to evaluate the immunogenicity in subjects

who had Visit 3 and 5 performed within the study windows [14-28 days], as specified in Protocol version 1 amendment 2.

15.1. Primary Immunogenicity

15.1.1. Primary Immunogenicity Variables & Derivations

The primary immunogenicity endpoints are:

- Vaccine-homologous HI titers at Day 43 (GMTs)
- Vaccine-homologous HI titers increase at Day 43 compared to visit 1 (Geometric Mean Fold Rise [GMFR])
- Seroprotection (SP) defined as titer ≥ 1:40 at Day 43 (percentage of participants meeting SP criteria)

See section 7.4 for details on the handling of multiple primary endpoints.

15.1.2. Intercurrent Event Handling and Data Imputation for Primary Immunogenicity Variables

Missing data will not be replaced. Refer also to PPS in section 5.6 and estimand section 2.4.

15.1.3. Primary Analysis of Primary Immunogenicity Variables

The primary immunogenicity endpoints will be analyzed, for the PPS, as follows:

- GMTs, with 95% CIs, will be calculated for each study intervention group for vaccine-homologous H5N8 HI titer at Day 43.
- GMFR at Day 43, compared to pre-vaccination, will be calculated for each study intervention group for vaccine-homologous H5N8 HI titer at Day 43 with 95% CIs.
- The CIs for GMT and GMFR and will be derived from an ANCOVA model on log-transformed titer. This model will include the dose group effect (i.e., 4 dose groups) as a fixed effect and the log-transformed titer pre-dose 1 (Day 1) as a covariable.
- HI SP, defined as meeting vaccine-homologous H5N8 HI titer ≥ 1:40, will be analyzed by reporting SPR.

SPR is defined as the percentage of participants who meet the SP definition and will be reported at Day 43 with Clopper-Pearson exact two-sided 95% CIs for each study intervention group.

15.2. Secondary Immunogenicity

15.2.1. Secondary Immunogenicity Variables & Derivations

The secondary immunogenicity endpoints are:

- Vaccine-homologous H5N8 HI titers at Day 1, 22, and 6 months post dose 2 (GMT).
- Vaccine-homologous N5N8 HI titers increase from pre-vaccination at Day 22, and 6 months post dose 2 (GMFR)
- SP, defined as titer ≥ 1:40 at Day 1, 22, and 6 months post dose 2 (percentage of participants meeting SP criteria)
- HI seroconversion (SC, defined as titer ≥ 1:40 for participants with pre-vaccination titer below 1:10 or as ≥ 4-fold increase from pre-vaccination titer to Day 1, 22, 43 and 6 months post dose 2 for participants with pre-vaccination titer ≥ 1.10 (percentage of participants meeting SC criteria).
- Vaccine-homologous H5N8 MN titers at Day 1, 22, 43, and 6 months post dose 2 (GMT)
- Seropositivity rates defined as percentage of participants with reciprocal titer greater than or equal to the LLOQ at Days 1, 22, 43, and 6 months post dose 2 (percentage of seropositive participants)
- MN vaccine response (VR) defined as titer ≥ 4 x LLOQ for participants with pre-vaccination titer below LLOQ or a ≥ 4-fold increase in titer for participants with pre-vaccination titer ≥ LLOQ at Days 22, 43, and 6 months post dose 2 (percentage of participants meeting VR criteria). Neutralization titers below the LLOQ of the assay are given an arbitrary value of half the LLOQ for the purpose of vaccine response calculation.

15.2.2. Intercurrent Event Handling and Data Imputation for Secondary Immunogenicity Variables

Missing data will not be replaced. Refer also to PPS in section 5.6 and estimand section 2.4.

15.2.3. Analysis of Secondary Immunogenicity Variables

The secondary immunogenicity endpoints will be analyzed as follows:

- GMTs, with 95% CIs, will be calculated for each study intervention group for vaccine-homologous H5N8 HI titer at Day 1, 22, and 6 months post dose 2. Results will be tabulated and presented graphically (in log10 scale). H5N8 HI titer will also be displayed using reverse cumulative distribution curves.
- GMFR from pre-vaccination, will be calculated for each study intervention group for vaccine-homologous H5N8 HI titer at Day 22, and 6 months post dose 2 with 95% CIs.
- The CIs for GMT/GMFR at post-vaccination timepoints will be derived from an ANCOVA model on log-transformed titer. This model will include the dose group effect (i.e., 4 dose groups) as a fixed effect and the log-transformed titer pre-dose 1 (Day 1) as a covariable. For GMT at Dose 1, t-student CI will be used. Results will be tabulated and presented graphically (in log10 scale).
- SP, defined as HI titer ≥ 1:40, will be analyzed by reporting SPR. SPR is defined as the percentage of participants who meet the SP definition and will be reported at Day 1, 22, and 6 months post dose 2, with Clopper-Pearson exact two-sided 95% CIs for each study intervention group.
- SC is defined as meeting vaccine-homologous H5N8 HI titer ≥1:40 in the serum of participants with visit 1pre-vaccination titer below 1:10 or as a ≥4-fold rise in post-vaccination HI titer with pre-vaccination titer ≥1:10 and will be analyzed by reporting SCR. SCR is defined as the percentage of participants who meet the SC definition and will be reported at Day 22, Day 43 and 6 months post dose 2, with Clopper-Pearson exact two-sided 95% CIs for each study intervention group. Results will be tabulated and presented graphically.
- For a subset of participants with Microneutralization (MN) titers, the following aggregate variables will be calculated for each study intervention group for vaccine-homologous H5N8 MN neutralization titer.
- GMTs and GMFR, with two-sided 95% CIs, will be calculated for each study intervention group for vaccine-homologous H5N8 MN titer at Day 1, 22, 43, and 6 months post dose 2. Results will be tabulated and presented graphically (in log10 scale).
- H5N8 HI & MN neutralization titer will also be displayed using reverse cumulative curves with all timepoints/groups in the same figure for each assay separately.
- Seropositivity rates will be summarized as the percentage of participants with seropositive results at Days 1, 22, 43, and 6 months post dose 2 (percentage of seropositive participants) with Clopper-Pearson exact two-sided 95% CIs for each study intervention group.
- MN VR will be analyzed as vaccine response rate (VRR). VRR is defined as the percentage of participants who meet the VR criteria and will be reported at Days 22, 43, and 6 months post dose 2 with Clopper-Pearson exact two-sided 95% CIs for each study intervention group. Results will be tabulated and presented graphically.

16. SAFETY OUTCOMES

All outputs for solicited events will be based on the DS. All other safety outcomes will be based on the ES.

There will be no statistical comparisons between the study intervention groups for safety data.

Primary Safety Endpoints
Solicited events

- Percentage of participants reporting each solicited administration site event (pain, erythema / redness, swelling) with onset within 7-days (i.e., day of vaccination and 6 subsequent days) following each vaccination and overall.
- Percentage of participants reporting each solicited systemic event (fatigue, fever, headache, muscle ache, joint pain, shivering [chills], sweating, nausea, vomiting, diarrhea, abdominal pain) with onset within 7-days (i.e., day of vaccination and 6 subsequent days) following each vaccination and overall.

Laboratory tests

- Percentage of participants with occurrence of toxicity grade increase in either hematology or biochemistry laboratory tests from baseline to 7 days after each vaccination (change in baseline)
- Shift table for toxicity grading in hematology or biochemistry laboratory tests from baseline to 7 days to 7 days after each vaccination (change in baseline)

Unsolicited events

- Percentage of participants reporting unsolicited adverse events within 21 days (i.e., day of vaccination and 20 subsequent days) following each vaccination and overall.

Medically attended adverse events (MAEs)

- Percentage of participants reporting MAEs for 21 days (i.e., day of vaccination and 20 subsequent days) after each vaccination, through 6 months post dose 2, and overall.

Serious adverse events (SAEs)

- Percentage of participants reporting SAEs until Day 43 and also 6 months post dose 2 following each vaccination and overall.

Potential immune-mediated disease (pIMDs)

- Percentage of participants reporting pIMDs until Day 43 and also 6 months post dose 2 following each vaccination and overall.

16.1. Adverse Events

Adverse Events (AEs) will be coded using MedDRA central coding dictionary, version 25.1 or higher. Adverse events will be described using frequency and percentage.

Adverse Events will be grouped by SOC, HLT and PT and summarized by study intervention at time of onset of the AE. The summary tables will present the number and percentage of total participants and number of events, by SOC and by PT for each study intervention.

For the summaries of AEs, participants who experience the same AE (in terms of the MedDRA SOC, HLT and PT) more than once will only be counted once for that event in the number of participants but all occurrences of the same event will be counted in the number of events.

Causality, as indicated by the Investigator is classed as "related" and "not related" to Q-Pan H5N8 vaccine. A "related" AE is defined as an AE with a relationship to study intervention. If a participant reports the same AE more than once within that SOC / PT, the AE with the worst-case relationship to study intervention will be used in the corresponding relationship summaries for each study intervention.

See APPENDIX 2 for handling of partial dates for AEs.

16.1.1. Solicited Adverse Events

Solicited administration site events and solicited systemic events to be summarized are included in Table E. Intensity scales for solicited events (administration site and systemic) are included in Table F and Table G.

Table E: Solicited events

Solicited administration site events	Solicited systemic events

Pain at Injection Site Erythema / Redness at Injection Site Swelling at Injection Site	Fever Headache Fatigue Muscle ache Joint pain Shivering (chills) Sweating Nausea Vomiting Diarrhea Abdominal pain

Table F: Intensity scales for solicited events in adults 18 years of age or older

Adults (≥18 years)		
Event	**Intensity grade**	**Parameter**
Pain at administration site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal everyday activities.
	2	Moderate: Painful when limb is moved and interferes with everyday activities.
	3	Severe: Significant pain at rest. Prevents normal everyday activities.
Headache	0	Normal
	1	Mild: Headache that is easily tolerated.
	2	Moderate: Headache that interferes with normal activity.
	3	Severe: Headache that prevents normal activity.
Fatigue	0	Normal
	1	Mild: Fatigue that is easily tolerated.

Adults (≥18 years)		
Event	**Intensity grade**	**Parameter**
	2	Moderate: Fatigue that interferes with normal activity.
	3	Severe: Fatigue that prevents normal activity.
Muscle ache all over body	0	Normal
	1	Mild: Muscle aches that are easily tolerated.
	2	Moderate: Muscle aches that interfere with normal activity.
	3	Severe: Muscle aches that prevent normal activity.
Joint pain	0	Normal
	1	Mild: Joint pain that is easily tolerated.
	2	Moderate: Joint pain that interferes with normal activity.
	3	Severe: Joint pain that prevents normal activity.
Shivering (chills)	0	Normal
	1	Mild: Shivering (chills) that is easily tolerated.
	2	Moderate: Shivering (chills) that interferes with normal activity.
	3	Severe: Shivering (chills) that prevents normal activity.
Sweating	0	Normal
	1	Mild: Sweating that is easily tolerated.
	2	Moderate: Sweating that interferes with normal activity.
	3	Severe: Sweating that prevents normal activity.
Gastrointestinal symptoms: nausea, vomiting, diarrhea and/or abdominal pain	0	Normal
	1	Mild: Gastrointestinal symptoms that are easily tolerated.
	2	Moderate: Gastrointestinal symptoms that interfere with normal activity.
	3	Severe: Gastrointestinal symptoms that prevent normal activity.
Redness at administration site		Record greatest surface diameter in mm

Adults (≥18 years)		
Event	**Intensity grade**	**Parameter**
Swelling at administration site		Record greatest surface diameter in mm
Temperature		Record temperature in °C/°F. Oral route is preferred.

Table G: Intensity scales for solicited events – erythema / swelling and fever

	Erythema/swelling	Fever (Temp °C)
0:	≤20 mm	<38.0 °C (<100.4 °F)
1:	> 20 - ≤50 mm	≥38.0 °C (100.4 °F) - ≤38.4 °C (101.2 °F)
2:	> 50 - ≤100 mm	≥38.5 °C (101.3 °F) - ≤38.9 °C (102.1 °F)
3:	>100 mm	≥39.0 °C (102.2 °F) - ≤ 40.0 °C (104.0 °F)
4:		>40.0 °C (104.0 °F)

Solicited events will be summarized and listed as:

- The number and percentage of participants, with exact 95% CIs, reporting each individual solicited administration site AE (pain, erythema/swelling, swelling) for all grades, grade ≥ 2, grade ≥ 3, medically attended events during the 7-day follow-up period, and ongoing at the end of the 7-day follow-up period will be tabulated following each vaccination and overall.
- The number and percentage of participants, with exact 95% CIs, reporting each individual solicited systemic AE (fatigue, fever, headache, muscle ache, joint pain, shivering [chills], sweating, gastrointestinal symptoms [nausea, vomiting, diarrhea, abdominal pain]) for all grades, grade ≥ 2, grade ≥ 3, medically attended events during the 7-day follow-up period, and ongoing at the end of the 7-day follow-up period will be tabulated following each vaccination and overall.
- The number and percentage of participants, with exact 95% CIs, reporting any solicited administration site AE, any solicited systemic AE and any solicited AE (across all administration site and systemic symptoms), for all grades, grade ≥ 2, grade ≥ 3, medically attended events during the 7-day follow-up period will be tabulated following each vaccination and overall.

- Duration of solicited events reported during the 7-day follow-up period will be tabulated for each individual solicited event using descriptive statistics (mean, minimum, Q1, median, Q3, maximum).. The start date is the first during the 7-day solicitation period with the symptom at grade > 0 while the stop date is the last day with the symptom at grade > 0 in or beyond the solicited period. In addition, the duration for specific grade(s) (grade ≥ 2, grade ≥ 3 and medically attended solicited events) for each symptom defined as the number of days in the reporting period with grade above or equal to specific grade will be summarized.

- All solicited administration site events will be included in a listing. Prolonged solicited AEs that continue beyond the 7-day follow-up period will be identified using a flag in the listing of solicited administration site events.

- All solicited systemic events will be included in a listing. Prolonged solicited AEs that continue beyond the 7-day follow-up period will be identified using a flag in the listing of solicited systemic events.

16.1.2. Unsolicited Adverse Events

All unsolicited adverse events summaries will be reported by MedDRA, SOC and PT and will include non-serious unsolicited events, SAE and AESI. These summaries will exclude solicited AE starting within day 1 to 7 and continuing beyond day 7.
The verbatim reports of unsolicited AEs will be reviewed by a physician and the signs and symptoms will be coded according to the MedDRA Dictionary for Adverse Reaction Terminology version 25.1 or higher. Every verbatim term will be matched with the appropriate Preferred Term.

Unsolicited events will be summarized and listed as:

The number and percentage of participants, with exact 95% CIs, with any unsolicited AEs during the 21-day follow-up period (i.e., the day of vaccination and 20 subsequent days) will be tabulated following each vaccination and overall.

This summary will be repeated for:

- grade ≥ 3 unsolicited AEs,
- causally related unsolicited AEs
- causally related and grade ≥ 3 unsolicited AEs,

- unsolicited AEs resulting in a medically attended visit

A list of unsolicited AEs leading to study discontinuation or vaccine discontinuation will be tabulated by study intervention group by MedDRA, SOC and PT.
All unsolicited AEs will be included in a listing.

16.1.3. Solicited and Unsolicited Adverse Events

For clinicaltrials.gov and EudraCT posting purposes, the following summary will be produced:
The number and percentage of participants reporting any unsolicited adverse events with MedDRA PTs that are synonymous with solicited events, and starting after the end of each solicited period, will be summarized following each vaccination and overall and by severity (mild, moderate or severe). If a participant experiences an event on more than one occasion, the maximum intensity will be reported. **Error! Reference source not found.** shows the corresponding MedDRA LLTs that will be selected from the unsolicited adverse events for this analysis.

Table H: Solicited events lower level term codes and decodes

Solicited event	Lower level term code	Corresponding Lower level term decode
Pain	10022086	Injection site pain
Erythema	10022061	Injection site erythema
Swelling	10053425	Injection site swelling
Fever	10016558	Fever
Headache	10019211	Headache
Fatigue	10016256	Fatigue
Myalgia	10028411	Myalgia
Arthralgia	10003239	Arthralgia
Chills	10008531	Chills
Nausea	10028813	Nausea
Vomiting	10047700	Vomiting
Diarrhoea	10012735	Diarrhoea
Abdominal pain	10000081	Abdominal pain

The number and percentage of participants, with exact 95% CIs, of combined solicited and unsolicited non-serious adverse events (all grades, Grade 3, medically attended) during the 21-day follow-up period (i.e., the day of

vaccination and 20 subsequent days) will be produced by SOC and PT, according to occurrence of each event, following each vaccination and overall. The number of events will also be provided in which 2 events are considered different if they have different start date or PT name.

16.1.4. Serious Adverse Events

SAEs will be summarized and listed as:

- The number and percentage of participants, with exact 95% CIs, with at least one report of SAE with onset after each vaccine administration up to Day 43 and up to study end (i.e., 6 months post-last vaccination) will be summarized.
  - This summary will be repeated for:
    - Causally related SAEs
    - Fatal SAEs
    - Causally related fatal SAEs
    - All SAEs will be included in a listing.

16.1.5. pIMDs

pIMDs will be summarized and listed as follows:

- The number and percentage of participants, with exact 95% CIs, with at least one report of pIMDs (all pIMDs, causally related) with onset after each vaccination administration up to Day 43 and up to study end (i.e., 6 months post-last vaccination) will be summarized.
- All pIMDs will also be described in detail in a tabular listing. Classification by new onset vs exacerbations of pIMDs will also be presented.

16.2. Laboratory Assessments Events

Laboratory assessments, including CBER grading derivations, to be assessed at Visits 2 and 4 (7 days after each vaccination) are listed in protocol Table 11. These laboratory assessments will be performed for the first 50% of enrolled participants in each age and dose group.

The percentage of participants with an increase in laboratory toxicity grading from baseline after each vaccination

and across vaccinations will be provided with Clopper-Pearson exact 95% CIs. This will be done for each safety laboratory test and across laboratory tests for exposed participants with safety laboratory results available after each vaccination and across vaccination.

Listings will be produced for laboratory assessments.

17. DATA NOT SUMMARIZED OR PRESENTED

The other variables and/or domains not summarized or presented are:

- Physical Examination, pregnancy test

These domains and/or variables will not be summarized or presented, but will be available in the clinical study database, SDTM and/or ADaM datasets.

18. REFERENCES

Clopper CJ, Pearson E. The Use of Confidence or Fiducial Limits Illustrated in the case of the Binomial. Biometrika. 1934;26:404-13.

Nauta J. Statistics in Clinical Vaccine Trials. 2010. Heidelberg: Springer.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

IQVIA Output Conventions

Outputs will be presented according to the following:

Document Headers
All TFL is to include the following header:
Vaccine: FLU Q-PAN H5N8
Study 219833 – DELIVERY DESIGNATION

where delivery designation is the name of the current delivery, e.g., DRY RUN, INTERIM ANALYSIS, FINAL ANALYSIS, etc.

Dates & Times

Depending on data available, dates and times will take the form yyyy-mm-ddThh:mm:ss.

Spelling Format

English US

Presentation of Study Intervention Groups

For outputs, intervention groups will be represented as follows and in the given order:

Study Intervention Group	For Tables and Figures	For Listings (include if different to tables)
3.75 µg HA + $AS03_B$	375_B	375_B
3.75 µg HA + $AS03_A$	375_A	375_A
7.5 µg HA + $AS03_B$	750_B	750_B
7.5 µg HA + $AS03_A$	750_A	750_A

Presentation of Visits

For outputs, visits will be represented as follows and in that order:

Long Name (default)	Short Name
Visit 1 (Day 1)	Day 1
Visit 2 (Day 8)	Day 8
Visit 3 (Day 22)	Day 22
Visit 4 (Day 29)	Day 29
Visit 5 (Day 43)	Day 43
Visit 6 (6 months post dose 2)	Day 183

Listings

All listings will be ordered by the following (unless otherwise indicated in the template):

- Randomized study intervention group (or intervention received if it's a safety output), in the order of 375_B, 375_A, 750_B, 750_A
- Center-participant ID,
- Date (where applicable).

DECIMAL PLACES

Decimal places for categorical data

- For percentages one decimal will be displayed
- Differences in percentages and their corresponding confidence limits will be displayed with one more decimal than the maximum number used to display the individual percentages, for example the difference between two percentages displayed with one decimal will be displayed with two decimals.

Decimal places for Demographic and baseline characteristics will be as follows:

The mean, median, and SD for continuous baseline characteristics (age) will be presented with one decimal.

Serological Summary Statistics

The number of decimals used when displaying GMTs and their CIs is shown in the following table:

GMT value	Number of decimals
<0.1	3
>=0.1 and <10	2
>=10 and <1000	1
>=1000	0

When multiple categories of GMT values are present in the same table, the number of decimals displayed should match that of the smallest category (i.e., the one with the higher number of decimals). For example, if GMT values of <0.1 appear in the same table as values of >=0.1 and <10, 3 decimals should be displayed for both.

- GMT ratios and their confidence limits will be displayed with 2 decimals regardless of the actual values.

APPENDIX 2. PARTIAL DATE CONVENTIONS

When partially completed dates (i.e., dates missing a day and/or month) are used in calculations, the following standard rules will be applied:

- A missing day will be replaced by 15
- A missing day and month will be replaced by June 30th.

The following exceptions apply:
When partially completed dates (i.e., with missing day or month) are used in calculations, the following rules will be applied:

- AE start dates with missing day:
  - If the month is not the same as the vaccine dose, then the imputed start date will be the 1st of the month.
  - If the event starts in the same month as the vaccine dose, the flag indicating if the event occurred before or after vaccination (AE.AESTRTPT) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the vaccine dose given during that month. If 'before vaccination' is selected, the imputed date will be one day before the vaccine dose given during that month.
- AE start dates with missing day and month:
  - If the year is not the same as the vaccine dose, then the imputed start date will be the 1st of January.
  - If the event starts in the same year as the vaccine dose, the flag indicating if the event occurred before or after vaccination (AE.AESTRTPT) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the first vaccine dose given during that year. If 'before vaccination' is selected, the imputed date will be one day before the first vaccine dose given during that year.
- AE end dates with missing day: the imputed end date will be the last day of the month or the study conclusion date whichever comes first.
- AE end dates with missing day and month: the imputed end date will be the last day of the year (31st of December) or the study conclusion date whichever comes first.

AE end dates with missing day, month and year: the imputed end date will be the study conclusion date.

All incomplete concomitant medication/vaccination start/end date will follow the rules above.

Imputed dates will NOT be presented in the listing.

DocuSign

Certificate Of Completion

Envelope Id: PPD
Status: Completed
Subject: Complete with Docusign: GSK H5N8-219833_SAP_v5.0_19AUG2024.pdf
Project Code (Enter 0 for non-billable projects): HAB99808
IQVIA ID (Login ID): PPD
Business Unit:
Other R&DS
Source Envelope:
Document Pages: 57
Signatures: 2
Envelope Originator:
Certificate Pages: 5
Initials: 0
PPD
AutoNav: Enabled
One IMS Way
EnvelopeId Stamping: Disabled
Plymouth Meeting, 19462
Time Zone: (UTC-08:00) Pacific Time (US & Canada)
PPD
IP Address: PPD

Record Tracking

Status: Original
8/20/2024 8:28:25 AM
Holder: PPD
PPD
Location: DocuSign

Signer Events	Signature	Timestamp
PPD PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 8/20/2024 8:33:34 AM Viewed: 8/20/2024 7:59:03 PM Signed: 8/20/2024 7:59:57 PM
Electronic Record and Signature Disclosure: Accepted: 10/28/2021 5:12:02 AM ID: PPD		
PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 8/20/2024 8:33:34 AM Viewed: 8/20/2024 8:33:46 AM Signed: 8/20/2024 8:34:21 AM
Electronic Record and Signature Disclosure: Accepted: 1/12/2022 4:05:57 AM ID:PPD		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	8/20/2024 8:33:34 AM
Certified Delivered	Security Checked	8/20/2024 8:33:46 AM
Signing Complete	Security Checked	8/20/2024 8:34:21 AM
Completed	Security Checked	8/20/2024 7:59:57 PM

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

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Operating Systems:	Windows® 2000, Windows® XP, Windows Vista®; Mac OS® X
Browsers:	• Internet Explorer (Windows Only) 8.0 or above – compatibility mode is supported only for 9.0 and above. • Windows Edge Current Version • Mozilla Firefox Current Version • Safari (Mac OS only) 6.2 or above • Google Chrome Current Version
PDF Reader:	Acrobat® or similar software may be required to view and print PDF files
Screen Resolution:	1024 x 768 Recommended
Enabled Security Settings:	Allow per session cookies
Mobile Signing:	• Apple iOS 7.0 or above • Android 4.0 or above

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Pre-release (e.g. beta) versions of operating systems and browsers are not supported.

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