TITLE PAGE

Protocol Title:

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

Protocol Number: 219833

Abbreviated Title: FLU Q-PAN H5N8=AS03-001

Study Phase: I/II

Sponsor Name: GlaxoSmithKline

Legal Registered Address:

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Date of Original Protocol: 03 May 2023

Date of Protocol Amendment 1.0: 23 June 2023

Date of Protocol Amendment 2.0: 22 August 2023

Date of Protocol Amendment 3.0: 16 February 2024

Approval Date: 16 February 2024

Sponsor Signatory

Pascal Peeters **Sr Dir. Clinical Project Lead** **Clinical Sc. Respiratory & Global Health**	**Date**

Medical Monitor name and contact information will be provided separately.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY			
Document	**Date**	**Substantial**	**Region**
Amendment 3.0	16 February 2024	Yes	Global
Amendment 2.0	22 August 2023	Yes	Global
Amendment 1.0	23 June 2023	Yes	Global
Original Protocol	03 May 2023	-	-

Amendment 3.0: 16 February 2024

Overall Rationale for the Amendment 3.0:

This protocol has been amended to extend the visit windows to ensure data is included in the Per Protocol Set (PPS) analysis given the large number of participants whose Visit 3 or Visit 5 was out of window. In this amendment, text from the updated GSK protocol template regarding publication policy has been added, and a correction to the number of times each serum sample will be tested in the same assay has been made in the hemagglutination inhibition assay section. The list of medical conditions considered to represent potential immune-mediated diseases (pIMDs) has been updated to the Standard MedDRA query for Immune-mediated/autoimmune diseases at the request of the FDA. Finally due to late availability of Day 43 immunogenicity data a preliminary analysis of safety data up to Day 43 has been added.

Added text in ***bold italic***, deleted text in ~~strikethrough~~.

Section # and Name	**Description of Changes from Amendment 2.0 to Amendment 3.0**	**Brief Rationale**
Section 1.3 Schedule of Activities, Table 2 Interval Between Study Visits	Updated allowed interval range for Visit 1 → Visit 3 and Visit 3 → Visit 5: • 14 – ~~28~~ ***35*** days	To ensure data is included in the PPS analysis given the large number of participants whose Visit 3 or Visit 5 was out of window.
Section 9.1 Statistical Hypotheses	The following text was updated: ~~Null hypotheses will be assessed independently in each of the 4 dose groups using a Bonferroni adjustment to control the 2.5% type I error.~~	The update is done to adjust the large number of participants excluded from the PPS.

Section # and Name	Description of Changes from Amendment 2.0 to Amendment 3.0	Brief Rationale
	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 ~~0.625~~***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 ~~98.75~~***95***% confidence interval (CI) for the SPR meets or exceeds 70% for adults of 18 to 64 years of age. The LL of the ~~98.75~~***95***% CI for the SPR meets or exceeds 60% for adults ≥65 years of age.	
Section 9.2 Sample Size Determination	The following text was updated: A non-evaluable rate of ~~no more than 8% yields~~ ***23% and 30% in 18 to 64 years of age and ≥65 years of age groups, respectively yield*** an approximate sample size of ~~120~~ ***95*** evaluable participants per dose group (i.e., ~~60~~ ***50*** participants between 18 to 64 years of age and ~~60~~ ***45*** participants above 65 years of age in each dose group), giving ~~73.5~~***77.8***% overall power to fulfill the 2 SPR immunogenicity criteria in any ***in the first group that is 7.5 mcg antigen + AS03A*** ~~one of the 4 dose groups~~. This assumes that the SPR are truly 20% higher than the critical value (namely 90% for participants 18 to 64 years of age and 80% for	The update is done to adjust the large number of participants excluded from the PPS.

Section # and Name	Description of Changes from Amendment 2.0 to Amendment 3.0	Brief Rationale
	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.***	
Section 9.5.1.1 Interim Safety Analysis	Section 9.5.1.1 heading title was updated to: Interim **Safety** Analysis at Day 43.	Due to the delay in developing the Hemagglutination Inhibition assay, the interim analysis is split into 2 separate deliverables of safety data and immunological data.
	The following text was updated: • 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 ~~will be conducted~~. • 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~~.	Text was updated for conciseness.
	Added text: • ***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.***	Clarification of the expectations for the interim analysis of safety.
	Removed text: • ~~Analyses of cleaned immunogenicity data, for analysis of vaccine-homologous HI antibody titers and MN titers,~~	Text was moved to the newly-added Section 9.5.1.2, Interim Immunogenicity Analysis at Day 43.

Section # and Name	Description of Changes from Amendment 2.0 to Amendment 3.0	Brief Rationale
	~~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.~~	
Section 9.5.1.2 Interim Immunogenicity Analysis at Day 43	A new section, Interim Immunogenicity Analysis at Day 43, was added.	This analysis will inform on the safety of Egg-based AS03 H5N1 vaccine that will be used in case a Pandemic is declared.
	The following text was added: ***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.*** • ***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.***	
Section 10.1.12 Publication Policy	Added text: ***Where required by regulation, the names of the sponsor signatory and investigator signatory will be made public.*** ***GSK intends to make anonymized participant-level data from this study available to external researchers for scientific analyses***	Newly added text to the GSK protocol template v3 (dated 10Jan2024).

Section # and Name	Description of Changes from Amendment 2.0 to Amendment 3.0	Brief Rationale
	or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding. Data will be shared with researchers in a non-identifying way, and appropriate measures will be taken to protect PI; these measures will comply with data protection and privacy laws that apply.	
Section 10.2 Appendix 2: Clinical Laboratory Tests	Updated Hemagglutination Inhibition Assay process: Briefly, serum samples are first adsorbed with RBCs to remove non-specific agglutinins and then treated with receptor destroying enzyme overnight to remove non-specific inhibitors of the hemagglutination, then diluted to 1:10, and serial diluted 2-fold in ~~triplicate~~***duplicate*** from 1:10 to 1:10240." "Each ~~sera~~***serum*** sample will be tested in ~~triplicate~~***duplicate*** within the same assay. The ***final result corresponds to the GMT for the duplicate***~~3 titer results will be reported, as will the GMT for the triplicate~~.	Correction
Section 10.8 Appendix 8: List of Potential Immune-Mediated Diseases	Replaced GSK list of pIMD MedDRA Terms version 26.0 with version 26.1.	Updated list
Section 10.9 Appendix 9 Protocol and Amendment History	Updated Appendix 9 with Amendment 2.0 changes.	Version history
Global document updates	Version and summary of changes were revised.	Version control

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1.0 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

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, given as a two-dose series to adults 18 to 64 years of age and 65 years of age and older.

Rationale:

The emergence of a novel reassortant influenza A (H5N8) virus in Russia in December 2020 was associated with 7 human cases – none of which were symptomatic, and none resulted in death. However, this influenza virus was associated with a high mortality rate among birds. The likelihood of human infection is low at present, although previous infections in humans have been observed in China since 2014. The United States poultry population is currently experiencing a high number of avian flu cases, increasing the likelihood of an interspecies crossover event that will increase transmission and infection in humans. In any case, crossover events resulting in influenza strains capable of triggering epidemics like the 2009 swine flu epidemic are inevitable. The first human case of Highly Pathogenic Avian Influenza (HPAI)A(H5) virus in the United States was reported in late April 2022 and the virus has remained in wild bird flyways during the summer with the migrating birds already bringing it back into the country in fall 2022. This study tests a platform for H5N8 strains with the goal of providing additional public health preparedness and protection.

Vaccination is the primary control measure against the spread of influenza virus infection in humans. Efforts are, therefore, underway to develop vaccines that could mitigate the impact of an H5N8 pandemic. GlaxoSmithKline (GSK) will produce an investigational AS03-adjuvanted influenza A/Astrakhan/3212/2020-like (H5N8) virus vaccine and will conduct a clinical trial to assess the immunogenicity and safety of different formulations of an H5N8 split virus vaccine manufactured in GSK Biologicals' Québec facility, administered with AS03 adjuvant.

Objectives, and Endpoints:

Objectives	Endpoints (Population Summary)
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 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).
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:

Objectives	Endpoints (Population Summary)
	• 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). • 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; HA=hemagglutinin; HI=hemagglutination inhibition; H5N8=monovalent influenza A/Astrakhan/3212/2020-like; LLOQ=lower limit of quantitation; MAE=medically attended adverse event; MN=microneutralization; pIMD=potential immune-mediated disease; SAE=serious adverse event; SC=seroconversion; SP=seroprotection; SPR=seroprotection rate; US=United States; VR=vaccine response.

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

Overall Design:

Number of Participants:

This is a Phase I/II, observer-blind, randomized, age- stratified, multi-centric study with 4 parallel groups, which will be conducted in the US.

The study is planned to enroll approximately 520 participants randomly assigned to one of the 4 dose groups. Each of the 4 groups will be stratified by age 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 and older (approximately 50% of participants enrolled).

Intervention Groups and Duration:

Each participant will receive 2 intramuscular doses of study vaccine 21 days apart. Each participant will participate for 6 months after receipt of the second dose administered.

Study Groups (approximately 130 participants in each dose group):

Dose	Age Subgroup of Participants	Number of Participants (Total =520)
375_B: 3.75 µg HA and $AS03_B$	18 - 64 years of age ≥65 years of age	65 65
375_A: 3.75 µg HA and $AS03_A$	18 - 64 years of age ≥65 years of age	65 65
750_B: 7.5 µg HA and $AS03_B$	18 - 64 years of age ≥65 years of age	65 65
750_A: 7.5 µg HA and $AS03_A$	18 - 64 years of age ≥65 years of age	65 65

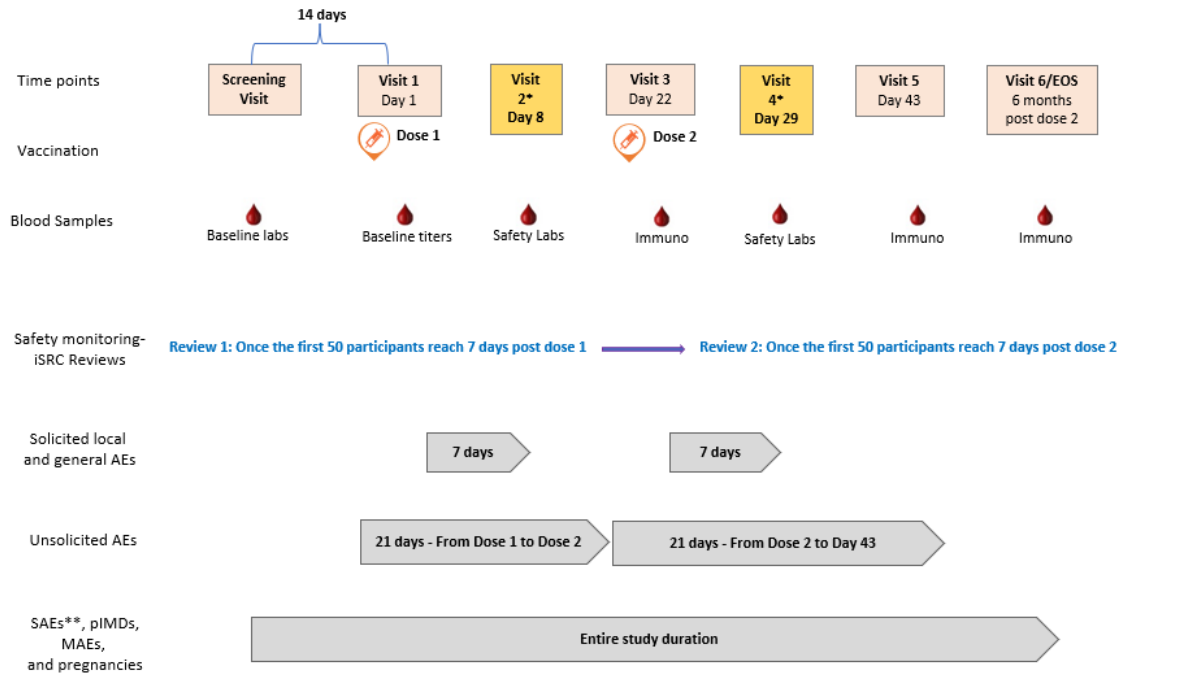
All the participants will have screening laboratory tests to determine eligibility for the study. The first 50% of enrolled participants in each age and dose group will be required to have on-site visits for safety laboratory tests 7 days after each vaccination (i.e., Visit 2 and Visit 4). All other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

Data Monitoring/Other Committee: None

Safety Monitoring: The study will be conducted with an internal Safety Review Committee.

1.2 Study Design

Figure 1 Study Design



*** 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 Visits**
**** 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.

1.3 Schedule of Activities

Table 1 Schedule of Activities

Time points	Screening Visit	Visit 1[1]	Visit 2[2]	Visit 3[1]	Visit 4[2]	Visit 5	Visit 6/EOS
		Day 1 Dose 1	Day 8-10	Day 22 Dose 2	Day 29-31	Day 43	6 months post dose 2
Informed consent	●						
Check inclusion/exclusion criteria	●	●		●			
Collect demographic data	●						
Study group and treatment number allocation		0					
Treatment number allocation for subsequent dose				0			
Recording of administered treatment number		●		●			
Blood sampling for hematology and biochemistry safety tests (approx. 10 mL for screening and approx. 6 mL for post-vaccination tests)[3]	●		●[2]		●[2]		
Blood sampling for immunogenicity assessments and HI/MN assay development/validation and samples for BARDA[4] (40 mL)		●[1]		●[1]		●	●
Vaccine administration		●		●			
30-minute observation period after each vaccine administration		●		●			
Medical history	●	●					
Physical examination[5]	●						
Vaccination history	●	●					
Urine pregnancy test to be performed prior to each vaccination (women of childbearing potential only)		●		●			
Check contraindications and warnings and precautions to vaccination		●		●			
Pre-vaccination body temperature		●		●			

Time points	Screening Visit	Visit 1[1]	Visit 2[2]	Visit 3[1]	Visit 4[2]	Visit 5	Visit 6/EOS
		Day 1 Dose 1	Day 8-10	Day 22 Dose 2	Day 29-31	Day 43	6 months post dose 2
Record any concomitant medication/vaccination	●	●		●		●	●
Distribution of diary cards		0		0			
Recording of solicited events (Up to 7 days after each vaccination)		●		●			
Recording of unsolicited adverse events (Up to 21 days after each vaccination)		●	●	●	●	●	
Return of diary cards			0	0	0	0	
Diary card transcription by investigator or delegate			●[6]	●	●[6]	●	
Reporting of SAEs, pIMDs, MAEs, pregnancies		●	●	●	●	●	●
Study Conclusion							●

Abbreviations: BARDA=Biomedical Advanced Research and Development Authority; eCRF=electronic case report form; EOS=end of study; FDA=Food and Drug Administration; HI=hemagglutination inhibition; MAE=medically attended adverse event; MN=microneutralization; pIMD=potential immune-mediated disease; SAE=serious adverse event.

Note: the double-line borders indicate analyses which will be performed on all data obtained up to those time points.

● is used to indicate a study procedure that requires documentation in the individual eCRF.

0 is used to indicate a study procedure that does not require documentation in the individual eCRF.

[1] All Day 1 and Day 22 activities, including blood draw, are to be performed prior to vaccine administration.

[2] The first 50% of study participants in each age and dose group will be required to have safety laboratory assessments performed at the clinic 7-days post 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.

[3] See Table 10 for applicable laboratory assessments.

[4] Participant will be asked in Informed Consent Form for permission for future use of blood samples, including use by BARDA.

[5] A physical examination based on medical history will be performed at the Screening Visit. Physical examination at each study visit after the study intervention administration visit will be performed only if the participant/participant's caregiver(s) indicates during questioning that there might be some underlying pathology(ies) or if deemed necessary by the investigator or delegate.

[6] Participants required to have safety laboratory measurements at Visits 2 and 4 will also have the initial data from their diary cards transcribed and then the diary card returned to them during these visits. All other participants will return their diary cards and have them transcribed on Visits 3 and 5.

Table 2 Interval 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

2.0 INTRODUCTION

2.1 Study Rationale

Novel influenza A viruses, including subtypes H5N1, H3N2v, H9N2, A(H1N1) pdm09, H7N9 and H5N8, continue to emerge and infect humans; therefore, it is imperative that preparation be maintained for the next influenza pandemic.

The US National Pre-Pandemic Influenza Vaccine Stockpile contains various influenza virus vaccines, including influenza A(H5) and A(H7) virus vaccines, as well as adjuvants, including AS03, for administration with the vaccine antigens to improve the immunogenicity and achieve antigen dose-sparing.

The emergence of a novel reassortant influenza A (H5N8) virus in Russia in December 2020 was associated with 7 human cases – none of which were symptomatic or associated with any deaths. However, this influenza virus was associated with a high mortality rate among birds.[1] The likelihood of human infection is low at present, although previous infections in humans have been observed in China since 2014.[2] The United States poultry population is currently experiencing a high number of avian flu cases, increasing the likelihood of an interspecies crossover event that will increase transmission and infection in humans. In any case, crossover events resulting in influenza strains capable of triggering epidemics like the 2009 swine flu epidemic are inevitable. This study tests a platform for H5N8 strains with the goal of providing additional public health preparedness and protection.[3]

The first human case of Highly Pathogenic Avian Influenza (HPAI)A(H5) virus in the United States was reported in late April 2022 and the virus has remained in wild bird flyways during the summer with the migrating birds already bringing it back into the country in fall 2022.[4] Therefore, it is crucial that preparation be maintained to enable rapid and successful process scale-up for commercial scale production if needed for an event. Antigenic analyses indicate that the candidate vaccine virus (CVV) A/Astrakhan/3212/2020-like (H5N8) influenza virus cross-reacts with the most recent A(H5) viruses from wild birds and poultry in the US, Europe, Africa, and Asia.

Vaccination is the primary control measure against the spread of influenza virus infection in humans. Efforts are, therefore, underway to develop vaccines that could mitigate the impact of an H5N8 pandemic. GSK will produce an investigational AS03-adjuvanted influenza A/Astrakhan/3212/2020-like (H5N8) virus vaccine and will conduct a clinical trial to assess the immunogenicity and safety of different formulations of an H5N8 split virus vaccine manufactured in GSK Biologicals' Québec facility, administered with AS03 adjuvant.

2.2 Background

Given the emergence of new influenza variants of concern and the ongoing need to match variants with vaccines, there is a critical need to ensure timely development of a H5N8 influenza vaccine.

Earlier studies have shown that the pandemic influenza vaccines administered with AS03 adjuvant had a similar safety profile wherein most of the adverse events occur around the time of vaccination. Review of data from these studies also suggests a favorable safety profile for adults over 65 years of age.

Furthermore, Biomedical Advanced Research and Development Authority (BARDA), in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID), has previously conducted 3 clinical studies (DMID 15-0064, DMID 15-0066, BARDA BPI 16005) using a non-GSK H5N8 antigen in combination with varying doses of either MF59 or GSK's AS03 as an adjuvant. These so-called 'mix and match' studies were completed in 2020, with DMID 15-0064 and 15-0066 together enrolling approximately 664 participants, of which 264 received an AS03-containing vaccine. The BPI 16005 study assessed the safety and immunogenicity of a homologous or heterologous vaccination series with inactivated monovalent influenza H5 vaccines (H5N1 and H5N8) and enrolled 720 participants. Data from these studies have showed that the vaccines were well tolerated in terms of safety profiles (follow-up period of up to 12 months period for the DMID studies and up to 17 months for the BARDA study). In terms of immunogenicity, these studies demonstrated that to achieve adequate immune responses, two doses of vaccines were required, and the immunogenicity was enhanced by the addition of $AS03_A$ adjuvant.[5,6]

GSK is planning to conduct a Phase I/II observer-blind, randomized, multi-center trial in 2023 to evaluate the safety and immunogenicity of different formulations of monovalent Influenza A/Astrakhan/3212/2020-like (H5N8) virus vaccine with the AS03 adjuvant system, given as a two-dose series to adults 18 to 64 years of age and 65 years of age and older.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of the study intervention may be found in the Investigator's Brochure (IB).

The Sponsor will immediately notify the Principal Investigator (PI) if any additional safety or toxicology information becomes available during the study.

This study will be performed in compliance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good

Clinical Practice (GCP), European Union Clinical Trials Regulation (EU CTR), and applicable regulatory requirements.

3.0 OBJECTIVES, AND ENDPOINTS

Objectives	Endpoints (Population Summary)
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 to 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 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).

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). • HI SC defined as titer ≥1:40 for participants with pre-vaccination titer below 1:10 or as 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; HA=hemagglutinin; HI=hemagglutination inhibition; H5N8=monovalent influenza A/Astrakhan/3212/2020-like; LLOQ=lower limit of quantitation; MAE=medically attended adverse event; MN=microneutralization; pIMD=potential immune-mediated disease; SAE=serious adverse event; SC=seroconversion; SP=seroprotection; US=United States; VR=vaccine response.

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

Note that complementary details on estimand such as impact of intercurrent events on the analysis can be found in Section 9.0.

4.0 STUDY DESIGN

4.1 Overall Design

The Study Design is provided in Figure 1. The Schedule of Activities is provided in Table 1.

This is a Phase I/II, observer-blind, randomized, age- stratified, multi-centric study with 4 parallel groups, which will be conducted in the US.

The study is planned to enroll approximately 520 participants randomly assigned to one of the 4 dose groups. Each of the 4 groups will be stratified by age 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 and older (approximately 50% of participants enrolled).

Each participant will receive 2 intramuscular doses of study vaccine 21 days apart. Each participant will participate for 6 months after receipt of the second dose administered.

Study Groups (approximately 130 participants in each dose group):

Dose	**Age Subgroup of Participants**	**Number of Participants (Total =520)**
375_B: 3.75 µg HA and $AS03_B$	18 - 64 years of age ≥65 years of age	65 65
375_A: 3.75 µg HA and $AS03_A$	18 - 64 years of age ≥65 years of age	65 65
750_B: 7.5 µg HA and $AS03_B$	18 - 64 years of age ≥65 years of age	65 65
750_A: 7.5 µg HA and $AS03_A$	18 - 64 years of age ≥65 years of age	65 65

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 on-site 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.

This study will be conducted with oversight by an internal Safety Review Committee (iSRC). See Section 10.1.7 for iSRC structure.

4.2 Scientific Rationale for Study Design

Novel influenza A viruses, including subtypes H5N1, H3N2v, H9N2, A(H1N1) pdm09, H7N9 and H5N8, continue to emerge and infect humans; therefore, it is imperative that preparation be maintained for the next influenza pandemic. The US National Pre-Pandemic Influenza Vaccine Stockpile contains various influenza virus vaccines, including influenza A(H5) and A(H7) virus vaccines, as well as adjuvants, including AS03, for administration with the

vaccine antigens to improve the immunogenicity and achieve antigen dose-sparing. The rationale for the study design is such that it allows the assessment of antigen sparing by varying the amount of adjuvant present, as well as assessing the effect of a change in antigen dose. It also further assesses any difference in immune response or safety profile in an older population (>65 years old) compared to a younger age subgroup (18 to 64 years old).

4.3 Justification for Dose

The rationale for evaluating 3.75 µg and 7.5 µg doses of the H5N8 antigen is based on the BARDA's requirement to assess the dose-sparing ability of full or half doses of AS03 in combination with Influenza A/Astrakhan/3212/2020-like (H5N8) virus vaccine, as well as previous experience with AS03 containing pandemic influenza vaccines. GSK has previously evaluated both 3.75 µg and 7.5 µg antigen doses in combination with the AS03 adjuvant in development of the H5N1 and H7N9 vaccines with a positive risk/benefit.

$AS03_A$ (11.86 mg tocopherol) and $AS03_B$ (5.93 mg tocopherol) will be evaluated in this study, since both AS03 formulations have been shown to improve the immunogenicity of inactivated split-virion H5N1 and H7N9 pandemic influenza vaccines in studies conducted by GSK.[7-14]

Further information on dose justification for this study can be found in the IB.

4.4 End of Study Definition

A participant is considered to have completed the study if he/she returned for the last visit as described in this protocol.

End of Study (EOS) is the last subject last visit (LSLV) (contact at 6 months post -last dose) or date of the last testing/reading released of the Human Biological Samples or imaging data, related to primary and secondary endpoints, whichever occurs later. End of study must be achieved no later than 8 months after LSLV. End of study cannot be before LSLV.

4.5 Study Stopping Criteria

Study stopping criteria is not applicable for this study. See holding rules in Section 8.4.

5.0 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Medically stable participants as established by medical history and clinical examination before entering into the study. (e.g., eligible participant should have no new diagnosis, escalation of treatment, or change in medication in the preceding 3 months).
2. A male or female ≥18 years of age at the time of signing consent form.
3. Participants, who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g., completion of the diary cards, return for follow-up visits, and return the diary cards in a timely manner).
4. Written or witnessed/thumb printed informed consent obtained from the participant prior to performance of any study specific procedure.
5. Female participants of childbearing potential or non-childbearing potential may be enrolled in the study if specific criteria are met. See Section 5.2.3 for details.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

5.2.1 Medical Conditions

1. Current diagnosis or history of autoimmune disorder(s) except hypothyroidism due to Hashimoto's thyroiditis. See Section 8.5.7.1.
2. History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine (including egg products).
3. Clinically significant acute or chronic pulmonary, cardiovascular, hepatic, or renal disease that appears uncontrolled or untreated, as determined by history or physical examination.
4. Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history, physical examination, or abnormalities in screening blood tests.
5. Recurrent history of or uncontrolled neurological disorders or seizures.
6. History of Guillain-Barré syndrome.
7. Diagnosed with cancer, or treatment for cancer within 3 years.
    - Persons with a history of cancer who are disease-free without treatment for 3 years or more are eligible.

- Persons with a history (within last 3 years) of histologically-confirmed basal cell carcinoma of the skin successfully treated with local excision only, are accepted and are eligible, but other histologic types of skin cancer are exclusionary.
- Women who are disease-free 3 years or more after treatment for breast cancer and receiving long-term prophylaxis (for example, with tamoxifen) are eligible.

8. Documented human immunodeficiency virus-positive participants.
9. Bedridden participants.
10. Personal or family history of narcolepsy.
11. FDA toxicity Grade 2 (Section 10.3), or greater, laboratory tests at Screening (Section 1.3).
12. Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the participant due to participation in the study.

5.2.2 Prior/Concomitant Therapy

13. Use of any investigational or non-registered product (drug, vaccine, or medical device) other than the study vaccine during the period beginning 30 days before the first dose of study vaccine (Day -29 to Day 1), or planned use during the entire study period.
14. Use of public health emergency vaccines like COVID-19, Monkey pox (mpox) etc. These can be given at any time, but there should a gap of 2 weeks before a dose of study vaccine can be given.
15. Use of any licensed vaccines: prior to receipt of the study vaccine (2 weeks for inactivated vaccines and 4 weeks for live vaccines) and continuing up to 3 weeks after receiving the dose 2 of study vaccine.
16. Administration of long-acting immune-modifying drugs at any time during the study period (e.g., infliximab).
17. Administration of immunoglobulins and/or any blood products or plasma derivatives during the period starting 3 months before the first dose of study vaccine or planned administration during the study period.
18. Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting 3 months prior to the first vaccine dose and through the entire study period. For corticosteroids, this will mean prednisone equivalent ≥20 mg/day for 14 days or a total of ≥280 mg of prednisone equivalent dose in any 14-day period. Inhaled and topical steroids are allowed.

5.2.3 Other Exclusions

19. Pregnant or lactating female.
20. Female planning to become pregnant or planning to discontinue contraceptive precautions within 2 months after completion of the vaccination series.

21. History of/or current drug/alcohol abuse.
22. Any study personnel or their immediate dependents, family, or household member.
23. Concurrently participating in another clinical study, at any time during the study period, in which the participant has been or will be exposed to an investigational or a non-investigational vaccine/product (drug or medical device).

5.3 Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently randomly assigned to study intervention/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

5.4 Criteria for Temporarily Delaying Enrollment and Vaccination

Vaccination may be postponed within the allowed time interval (Table 2) until transient circumstances cited below have been resolved:

- Acute disease and/or fever at the time of each vaccination: Fever is defined as a temperature of or above 38.0°C/100.4°F. The preferred route for measuring temperature in this study will be oral. Participants with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever may be enrolled at the discretion of the investigator.
- Use of antipyretics/analgesics (e.g., acetaminophen and non-steroidal anti-inflammatory drugs [NSAIDs]) and/or antibiotics within 3 days prior to vaccination. Low-dose aspirin (81 mg daily) regimen is permitted.
- Use of public health emergency vaccines like COVID-19, Monkey pox etc. These can be given at any time, but there should a gap of 2 weeks before a dose of study vaccine can be given.

6.0 STUDY INTERVENTIONS AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), intended to be administered to a study participant according to the study protocol.

6.1 Study Interventions Administered

Table 3 Study Interventions Administered

Study intervention Name:	**3.75 µg HA + AS03$_B$ ****		**3.75 µg HA + AS03$_A$ ***		**7.5 µg HA + AS03$_B$ ****		**7.5 µg HA + AS03$_A$ ***	
Vaccine Product Name:	FLU Q-PAN H5N8 (3.75)	AS03$_B$	FLU Q-PAN H5N8 (3.75)	AS03$_A$	FLU Q-PAN H5N8 (7.5)	AS03$_B$	FLU Q-PAN H5N8 (7.5)	AS03$_A$
Presentation:	Suspension for emulsion for injection in vial	Emulsion for emulsion for injection in vial	Suspension for emulsion for injection in vial	Emulsion for emulsion for injection in vial	Suspension for emulsion for injection in vial	Emulsion for emulsion for injection in vial	Suspension for emulsion for injection in vial	Emulsion for emulsion for injection in vial
Vaccine Product Formulation (refer to Pharmacy Manual):	A/Astrakhan/3212/2020-like (H5N8) (3.75 µg HA); Water for injection q.s.	AS03$_B$: DL-α-tocopherol and squalene in an o/w emulsion (5.93 mg DL-α-tocopherol); Water for injection q.s.	A/Astrakhan/3212/2020-like (H5N8) (3.75 µg HA); Water for injection q.s.	AS03$_A$: DL-α-tocopherol and squalene in an o/w emulsion (11.86 mg DL-α-tocopherol); Water for injection q.s.	A/Astrakhan/3212/2020-like (H5N8) (7.5 µg HA); Water for injection q.s.	AS03$_B$: DL-α-tocopherol and squalene in an o/w emulsion (5.93 mg DL-α-tocopherol); Water for injection q.s.	A/Astrakhan/3212/2020-like (H5N8) (7.5 µg HA); Water for injection q.s.	AS03$_A$: DL-α-tocopherol and squalene in an o/w emulsion (11.86 mg DL-α-tocopherol); Water for injection q.s.
Volume to be Administered:	0.25 mL		0.5 mL		0.375 mL		0.5 mL	
Number of Doses to be Administered:	2		2		2		2	
Route of Administration:	Intramuscular use							
Administration Site:								

Location:	Deltoid
Directionality:	Not applicable
Laterality***:	Non-dominant
Packaging and Labeling****:	Refer to Pharmacy Manual for more details
Manufacturer:	GSK Biologicals SA
Type of contact/Time points:	Visit 1 (Day 1), Visit 3 (Day 22)

Abbreviations: HA=hemagglutinin o/w=oil/water; q.s.=quantity sufficient.

* The $AS03_A$ doses will be prepared using adjuvant vialed at a concentration of 47.44 mg/mL tocopherol. The final $AS03_A$ doses will contain 11.86 mg tocopherol.

** The $AS03_B$ doses will be prepared as half a dilution of $AS03_A$ (with $AS03_A$ vialed at concentration of 47.44 mg/mL).

*** The non-dominant arm is the preferred arm of injection. In case it is not possible to administer the vaccine in the non-dominant arm, an injection in the dominant arm may be performed.

****Labeling is compliant with the requirements of applicable regulatory agencies.

6.2 Preparation, Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit and storage for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized study site staff may supply or administer study intervention.

All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study site staff.

The investigator is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

The investigator, a member of the study site staff, or a hospital pharmacist must maintain an adequate record of the receipt, distribution, and storage temperature of the study vaccine using the Drug Accountability Form. These forms must be available for inspection at any time.

Further guidance and information for the storage, handling, and final disposition of study interventions are provided in the Pharmacy Manual.

6.3 Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally assigned to randomized study intervention using an interactive web response system (IWRS). The randomization will be stratified by age subgroup and use a permutation blocking scheme. Before the study is initiated, the log-in information and directions for the IWRS will be provided to each study site.

Data will be collected in an observer-blind manner. The investigator(s), their staff and the participants will not be aware of the study intervention assignment. The study intervention will be prepared and administered by qualified study personnel who can be aware of the intervention assignment. The number of each intervention kit will be recorded in the eCRF.

The laboratory in charge of sample testing will be blinded to the study intervention assignment. Codes will be used to link the participant and study to each sample. There will be no link between the study intervention and the identity of the participant.

GSKs Global Safety staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant’s intervention assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and the eCRF. See Section 8.3 for pre- and post-vaccination procedures.

6.5 Dose Modification

Dose modifications are not applicable for this study.

6.6 Continued Access to Study Intervention After the End of the Study

Not applicable for this study.

6.7 Treatment of Overdose

For this study, an overdose is any dose of study intervention given to a participant that exceeds the maximum study dose for a single vaccination.

GSK does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

- Contact the medical monitor immediately.
- Evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the subsequent dose should be reduced.

6.8 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or other specific categories of interest that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency
- Route of administration
- For vaccines (if applicable) include brand name and manufacturer (plus lot number if available)

Concomitant therapy that meets the exclusionary criteria for this study is listed in Section 5.2.2.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7.0 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific study sites or of the study as a whole are detailed in Section 10.1.11.

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention refers to any participant who has received the first dose and has not received the second dose of study intervention. A participant who discontinued study intervention may continue other study procedures (e.g., safety assessment or immunogenicity testing), planned in the study protocol at the discretion of the investigator.

The primary reason for premature discontinuation of the study intervention will be documented on the eCRF as follows:

- AE requiring expedited reporting (i.e., SAE, potential immune-mediated disease [pIMD])
- Unsolicited non-serious AE
- Safety laboratory assessment results that are Grade 2 (moderate) or greater based on FDA toxicity grading that did not resolve, after repeat testing, to FDA toxicity Grade 1 or less (Figure 2)
- Solicited event
- Protocol Deviation
- Not willing to be vaccinated
- Pregnancy
- Inappropriate enrollment
- Other (specify)

It may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will be encouraged to remain in the study to be evaluated for post- dose visits and for safety follow-up. See the Schedule of Activities (SoA) in Section 1.3 for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Participants who discontinue study intervention will not be replaced.

7.1.1 Contraindications to Subsequent Study Intervention(s) Administration

The eligibility for subsequent study intervention administration must be confirmed before administering any additional dose.

Participants who meet any of the criteria listed below or criteria listed in Sections 5.2.1 and 5.2.2 should not receive additional doses of study intervention. Such participants should be encouraged to continue other study procedures. All relevant criteria for discontinuation of study intervention administration must be recorded in the eCRF.

- Participants who experience any SAE judged to be possibly or probably related to study intervention or non-study concomitant vaccine/product, including hypersensitivity reactions.
- Participants who develop any new condition which, in the opinion of the investigator, may pose additional risk to the participants if they continue to participate in the study.
- Anaphylaxis following the administration of study interventions.
- Any condition that in the judgment of the investigator would make intramuscular injection unsafe.
- Occurrence of a new pIMD that, in the opinion of the investigator, exposes the participant to unacceptable risk from subsequent vaccination. In such cases, the investigator should use their clinical judgment prior to administering the next dose of the study interventions. Refer to Section 8.5.7.1 for the definition of pIMD.
- Pregnancy.

7.2 Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request for any reason (or without providing any reason) or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.

Participants who discontinue study intervention or withdrawn from the study due to a safety issue are required to have a follow-up visit to monitor the status of the safety issue. Otherwise, the participant will be permanently discontinued from the study intervention and the study at that time.

All data and samples collected up to and including the date of withdrawal of/last contact with the participant will be included in the study analyses. If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

The primary reason for study withdrawal will be documented in the eCRF based on the list below:

- AE requiring expedited reporting (i.e., SAE, pIMD)

- Unsolicited non-serious AE
- Solicited events
- Protocol deviation
- Withdrawal by participant, not due to an AE*
- Migrated/Moved from the study area
- Lost to follow-up
- Sponsor study termination
- Inappropriate enrollment
- Other (specify)

*If a participant is withdrawn from the study because he/she has withdrawn consent and provided the reason for its withdrawal, the investigator must document this reason in the eCRF.

Participants who are withdrawn from the study because of SAEs/AEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigators will follow participants who are withdrawn from the study as result of an SAE/AE until the event is resolved (see Section 10.5.3).

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The study site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8.0 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with IQVIA immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures and associated data conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the informed consent form (ICF) may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA (Section 1.3).

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 240 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples (e.g., hemolyzed sample). Only one sample per timepoint should be sent to the laboratory for testing.

8.1 Screening Procedures

8.1.1 Informed Consent

The signed informed consent of the participant must be obtained before study participation. Refer to Section 10.1.4 for the requirement on how informed consent will be obtained.

8.1.2 Check Inclusion and Exclusion Criteria

All inclusion and exclusion criteria will be checked as described in Sections 5.1 and 5.2 at Screening Visits and before dosing on Visit 1 and Visit 3.

8.1.3 Collection of Demographic Data

Demographic data according to local regulations such as date of birth, sex, race*, ethnicity*, and occupation will be collected in the eCRF. Collection of sex, race, and ethnicity data is

necessary to assess and monitor the diversity of the trial participants, and to determine if the trial participants are truly representative of the impacted population.

*Differences in the safety and efficacy of certain medical products, including vaccines, have been observed in racially and ethnically distinct subgroups.[18-20] These differences may be attributable to intrinsic factors (e.g., genetics, metabolism, elimination), extrinsic factors (e.g., diet, environmental exposure, sociocultural issues), or interactions between these factors. Therefore, both geographic ancestry (race) and ethnicity will be collected for all study participants.

8.1.4 Medical History

The participant's medical history will be obtained by interviewing the participant and a review of the participant's available medical records. Any relevant pre-existing conditions, signs and/or symptoms present prior to the study intervention will be recorded in the eCRF.

8.1.5 Physical Examinations

Physical examination will be performed for each participant.

If the investigator determines that the participant's health on the day of study intervention administration temporarily precludes dosing, the visit will be rescheduled. Refer to the Section 5.4 for the list of criteria for temporary delay of study intervention administration. Treatment of any abnormality observed during this examination has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

Physical examination at each study visit after the Screening Visit will be performed only if the participant/participant's caregiver(s) indicates during questioning that there might be some underlying pathology(ies) or if deemed necessary by the investigator or delegate.

8.1.6 Medication and Vaccination History

The participant's medication and vaccination history will be obtained by interviewing the participant and review of the participant's available medical records.

Participant's vaccination history for prior 3 years should be collected.

8.1.7 Biological Samples for Screening

A volume of approximately 10 mL whole blood will be collected at the Screening Visit for the following laboratory assessments: Hematology: complete blood count with differential and platelet count; Chemistry/metabolic panel: Sodium, Potassium, Creatinine, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline Phosphatase, total bilirubin, and blood urea nitrogen (BUN). These laboratory assessments will be performed

locally at the site. Participants with laboratory assessment results of FDA toxicity Grade 1 or lower will be considered eligible to participate in the study (Section 10.3).

8.2 Immunogenicity Assessments

Collected biological samples will be used for protocol-mandated research and purposes related to the improvement, development, validation, and quality assurance of the laboratory tests described in this protocol and for transfer of sera samples to BARDA for future use, for those participants who consented their samples be utilized for further research.

Future findings may make it desirable to use the samples acquired in this study for future research not described in this protocol. All participants will be asked to give a specific consent to allow Sponsor or a contracted partner to use the samples for future research.

Future research will be subjected to prior Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approval if required per local legislation.

Information on further investigations and their rationale can be obtained from Sponsor.

Sample testing will be done in accordance with the recorded consent of the individual participant.

If additional testing is performed, the marker priority ranking given in Section 8.2.3 may be changed.

Collected samples will be stored at GSK for a maximum of 20 years. Samples at BARDA may be stored for 20 years and beyond. This storage period begins when the last participant performed the last study visit, unless local rules, regulations or guidelines require different timeframes or procedures, which would then be in line with participant consent. These extra requirements need to be communicated formally, discussed, and agreed to with GSK.

8.2.1 Biological Samples

A volume of 40 mL whole blood will be collected at Visits 1, 3, 5, and 6 to provide approximately 15 mL serum intended to be used for assay development/validation, protocol-mandated research and for transfer of sera samples to BARDA for future use (if consented by participant). The protocol-specified testing will be performed at GSK and/or GSK designated laboratories.

Prior to measurement of the immune response, collected blood samples will be used to enable the development and the validation of the assays used in this study (HI and MN).

8.2.2 Laboratory Assays

Table 4 Laboratory Assays

Test classification	System	Component	Method	Laboratory
Humoral Immunity	Serum	Inhibiting hemagglutination titers (A/Astrakhan/3212/2020-like (H5N8))	HI	GSK or GSK designated Lab**
	Serum (subset*)	Neutralizing titers (A/Astrakhan/3212/2020-like (H5N8))	MN	GSK or GSK designated Lab**

Abbreviations: H5N8=Influenza A/Astrakhan/3212/2020-like; HI=hemagglutination inhibition; MN=microneutralization.

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

** GSK laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium. CLS may designate testing to GSK Research laboratories in Rixensart, Belgium; Rockville, USA; Sienna, Italy, or to a contracted external partner laboratory.

Please refer to Section 10.2 for a brief description of the assays performed in the study.

The addresses of clinical laboratories used for sample analysis are provided in a separate document accompanying this study protocol.

GSK clinical laboratories have established a Quality System supported by procedures. The activities of GSK clinical laboratories and GSK designated labs (third parties) are audited regularly for quality assessment by an internal (Sponsor-dependent) but laboratory independent Quality Department.

8.2.3 Immunological Read-Outs

Table 5 Immunological Read-Outs

Blood sampling time point		Subset name	No. participants	Component	Components priority rank
Type of contact and timepoint	Sampling time point				
Visit 1 (Day 1)	Pre-Vacc I	HI	520	Vaccine-homologous (A/Astrakhan/3212/2020-like (H5N8))	1
Visit 1 (Day 1)	Pre-Vacc I	MN	260	Vaccine-homologous Influenza (A/Astrakhan/3212/2020-like (H5N8))	2
Visit 3 (Day 22)	Pre-Vacc II	HI	520	Vaccine-homologous Influenza (A/Astrakhan/3212/2020-like (H5N8))	1
Visit 3 (Day 22)	Pre-Vacc II	MN	260	Vaccine-homologous Influenza (A/Astrakhan/3212/2020-like (H5N8))	2
Visit 5 (Day 43)	Post-Vacc II	HI	520	Vaccine-homologous Influenza (A/Astrakhan/3212/2020-like (H5N8))	1
Visit 5 (Day 43)	Post-Vacc II	MN	260	Vaccine-homologous Influenza (A/Astrakhan/3212/2020-like (H5N8))	2
Visit 6 (6 months post dose 2)	Post-Vacc II	HI	520	Vaccine-homologous Influenza (A/Astrakhan/3212/2020-like (H5N8))	1
Visit 6 (6 months post dose 2)	Post-Vacc II	MN	260	Vaccine-homologous Influenza (A/Astrakhan/3212/2020-like (H5N8))	2

Abbreviations: HI=hemagglutination inhibition; MN=microneutralization; No.=number; vacc=vaccine.

8.2.4 Immunological Correlates of Protection

Although there is no accepted correlate of protection against influenza virus, either seasonal or pandemic, the protective role of antibodies against HA and, to a lesser extent, neuraminidase, is well established and has been demonstrated both in experimentally infected animals and humans.[15]

For this reason, the induction of HA-specific antibodies is used as a marker of potential vaccine efficacy and the serum HI assay is used to demonstrate this humoral response. Hemagglutination inhibition titers of 1:40 or greater have been associated with protection from influenza illness in at least 50% of participants in challenge studies and correlate with vaccine effectiveness.[16,17]

8.3 Pre- and Post- Vaccination Procedures

8.3.1 Check Inclusion and Exclusion Criteria

All inclusion and exclusion criteria will be re-checked as described in Sections 5.1 and 5.2 before dosing on Visit 1 and Visit 3.

8.3.2 Body Temperature

Body temperature must be assessed prior to study intervention administration and/or blood draw.

If the participant has fever (fever is defined as temperature ≥38.0°C [100.4°F] regardless of the location of measurement) on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit (Table 2).

If the investigator determines that the participant's health on the day of vaccination temporarily precludes vaccination, the visit will be rescheduled.

8.3.3 Pregnancy Testing

Female participants of childbearing potential must perform a urine pregnancy test prior to any study vaccine administration. Pregnancy testing must be performed even if the participant is menstruating at the time of the study visit. The study intervention may only be administered if the pregnancy test is negative.

Refer to the Section 10.6.2 for the information on study continuation for participant who becomes pregnant during the study.

8.3.4 Medical History

Changes or updates to participant medical history since Screening Visit will be recorded in eCRF.

8.3.5 Medication and Vaccine History

Changes or updates to participant medical history since Screening Visit will be recorded in eCRF.

8.3.6 Post-Vaccination Observation Period

Participants will undergo a 30-minute observation period immediately following administration of each dose of study vaccine, where they will be assessed by a qualified healthcare professional for any signs of any adverse events.

8.4 Safety Assessments

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE, SAE, or pIMD. The investigator and any designees remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study.

8.4.1 Safety Laboratory Assessments

At Visits 2 and 4, a whole blood sample of approximately 6 mL will be drawn from the first 50% of participants of each age/dose group for the following laboratory assessments: Hematology: complete blood count with differential and platelet count; Chemistry/metabolic panel: Sodium, Potassium, ALT, AST, Alkaline Phosphatase, total bilirubin, creatinine, and BUN.

The post-vaccination clinical safety laboratory assessments will be performed by a central laboratory as detailed in the Laboratory Manual. See Section 10.3 for the FDA Toxicity Grading Scale. See Section 10.4 for management of participants with abnormal laboratory values.

8.4.2 Study Holding Rules and Safety Monitoring

8.4.2.1 Internal Safety Review Committee

The study will also include 2 planned iSRC reviews. The iSRC reviews will occur after the safety data for the 7 days post dose 1of the first 50 participants have been recorded and are available. The second iSRC review will occur after the first 50 participants have completed 7 days post dose 2, and the safety data is available.

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.

8.4.2.2 Study Holding Rules

Holding rules in Table 6 will be assessed by each investigator on a continuous basis. Meeting any of these holding rules will trigger a hold of vaccination irrespective of number of participants enrolled and/or timing of the event.

Of note, no formal holding rules will be applied for other safety data. However, if available, these data will also be reviewed in order to allow an overall assessment of the benefit/risk ratio of vaccination.

If any investigator becomes aware of a holding rule being met, he/she will suspend vaccination and inform the medical monitor immediately.

Table 6 Study Holding Rules

Holding Rule	Event (per dose and per individual study group)	Number of Participants
1a	Death or any life-threatening SAE that cannot be reasonably attributed to a cause other than vaccination as per investigator or Sponsor assessment	≥1
1b	Any non-life-threatening SAE that cannot be reasonably attributed to a cause other than vaccination as per investigator or Sponsor assessment	≥1

Abbreviations: SAE=serious adverse event.

8.5 Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs can be found in Section 10.5.

The definitions of unsolicited and solicited events can be found in Section 10.5.1.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs until the event has resolved, subsided, stabilized, disappeared, or until the event is otherwise explained, or the participant is lost to follow-up, irrespective of seriousness or relatedness (see Section 7.0).

This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.5 and 10.5.3.

8.5.1 Time Period and Frequency for Collecting AE, SAE, pIMD, MAE Information

Serious AEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a

GSK product (non-IMP) will be recorded from the time a participant consents to participate in the study.

All SAEs (not related to study participation), pIMDs, medically attended adverse events (MAEs), and pregnancies will be collected from the start of study intervention until 6 months after the last vaccination at the time points specified in the SoA (Section 1.3).

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs.

All SAEs and pIMDs (pIMDs can be serious or non-serious) will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours of the investigator's awareness of the event, as indicated in Section 10.5.5. The investigator will submit any updated SAE or pIMD data to the Sponsor or designee within 24 hours of their awareness of the updated information.

All unsolicited AEs that occur within 21 days following administration of each dose of study intervention and MAEs that occur at any time during the study must be recorded onto the appropriate section of the eCRF, irrespective of their intensity or whether or not they are considered related to the study intervention.

All solicited events that occur within 7 days following administration of each dose of study intervention must be recorded into the diary, irrespective of intensity. All other AEs occurring within this time frame should be recorded on the appropriate section of the eCRF, irrespective of their intensity or whether or not they are considered related to the study intervention.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event/cause of death to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor or designee.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting safety reports are provided in Sections 10.5.3 and 10.5.5.

Table 7 Timeframes for Recording and Reporting Safety Information

Event	**Screening Visit**	**Pre-Dose**	**Visit 1**	**Visit 2* or Remote Visit**	**Visit 3**	**Visit 4* or Remote Visit**	**Visit 5**	**Visit 6 6 months post dose 2**
			Day 1 Dose 1	**Days 8-10**	**Day 22 Dose 2**	**Days 29-31**	**Day 43**	
Administration site and Systemic solicited events								
Unsolicited AEs								
AEs/SAEs leading to withdrawal from the study								
SAEs								
SAEs related to the study intervention								
Pregnancy								
All pIMDs								
MAEs								

Abbreviations: AE=adverse event; MAE=medically attended adverse event; SAE=serious adverse event; pIMD=potential immune-mediated disease.

* The first 50% of study participants in each age and dose group will be required to have safety laboratory assessments performed at the clinic 7-days post each vaccination (i.e., Visit 2 and Visit 4). All other participants will have a remote visit with the site.

8.5.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

Participants must be made aware of the requirement to report any new medical condition or worsening of any pre-existing medical condition requiring contact with a healthcare professional to the site staff.

8.5.2.1 Clinically Significant Abnormal Laboratory Findings

Post-vaccination clinical laboratory measurements (Section 8.4.1) are scheduled for the first 50% of participants enrolled in each age/dose group. These laboratory measurements may also be performed, and the results obtained as part of critical care or follow-up due to the occurrence of MAEs, SAEs, or pIMDs during the study.
The investigator must review the laboratory report, document that he/she did so, and record any clinically relevant changes occurring during the study in the eCRF. Clinically significant abnormal laboratory findings are those which are associated with an underlying disease judged by the investigator to be more severe than expected for the participant's condition. These results should be reported as an AE, MAE, SAE, or Adverse Events of Special Interest (AESI) as applicable for the study.
See Section 10.3 for the FDA Toxicity Grading Scale and Section 10.4 for the management of participants with abnormal laboratory values.

8.5.3 Treatment of Adverse Events

Any medication administered for the treatment of an SAE/pIMD should be recorded in the Expedited Adverse Events report of the participant’s eCRF screen.

8.5.4 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs (Section 10.5) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.5.

8.5.5 Regulatory Reporting Requirements for SAEs and Other Events

Prompt notification by the investigator to the Sponsor of an SAE or pIMD is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

For SAEs and pIMDs, the investigator must always provide an assessment of causality at the time of the initial report, as defined in the Section 10.5.3.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Table 8 Timeframes for Submitting SAE, Pregnancy, pIMDs to IQVIA

Type of event	Initial reports		Follow-up of relevant information on a previous report	
	Timeframe	**Documents**	**Timeframe**	**Documents**
SAEs	24 hours* ‡‡	Electronic‡ AEs Report	24 hours*	Electronic‡ AEs Report
Pregnancies	24 hours*	Electronic pregnancy report	24 hours *	Electronic pregnancy report
pIMDs (whether serious or non-serious)	24 hours** ‡‡	Electronic‡ AEs Report	24 hours*	Electronic‡ AEs Report

Abbreviation: AE=adverse event; SAE=serious adverse event; pIMD=potential immune-mediated disease.
* Timeframe allowed after receipt or awareness of the information by the investigator/site staff.
**Timeframe allowed once the investigator determines that the event meets the protocol definition of a pIMD.
‡ Paper AEs report may be submitted in the case that the electronic system is not functioning. The paper report will be dated and signed by the investigator (or designee). For each SAE/pIMD, the investigator(s) must document in the medical notes that they have reviewed the SAE/pIMD and have provided an assessment of causality.
‡‡ The investigator will be required to confirm review of the SAE/pIMD causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE/pIMD.

8.5.6 Pregnancy

Details of all pregnancies in study participants will be collected after the start of study intervention and until the outcome of the pregnancy is known. Female participants who become pregnant after the first study intervention dose must not receive the second dose of the study intervention but may continue other study procedures at the discretion of the investigator.

If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the Sponsor or designee within 24 hours of learning of the participant's pregnancy and should follow the procedures outlined in Section 10.5.3

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including if found in an aborted fetus, stillbirth, or neonatal death]) the investigator will report according to the SAE reporting procedures described in Section 10.5.5.

The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor or designee.

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the Sponsor as described in Section 8.5.5. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

8.5.7 Adverse Events of Special Interest

8.5.7.1 Potential Immune-Mediated Diseases

Potential immune-mediated diseases are a subset of AESIs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune etiology. Adverse events that need to be recorded and reported as pIMDs include those listed in Table 16 and must be reported in an expedited manner regardless of causality, seriousness, or medical opinion on etiology.

The investigator(s) must exercise their medical/scientific judgment to determine whether other diseases have an autoimmune origin (i.e., pathophysiology involving systemic or organ-specific pathogenic autoantibodies) and should also be recorded as a pIMD. In addition, the investigator should categorize each pIMD as a new onset condition (if it started following vaccination) in the eCRF.

8.5.8 Participant Card

The investigator (or designee) must provide the participant/participant's caregiver(s) with a "participant card" containing information about the clinical study. The participant/participant's caregiver(s) must be instructed to always keep the participant card in their possession for the duration of the study. In an emergency, this card serves to inform the responsible attending physician/caregiver/family member that the participant is in a clinical study and that relevant information may be obtained by contacting the investigator(s) or their back-up.

8.6 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.8 Genetics

Genetics are not evaluated in this study.

8.9 Biomarkers

Biomarkers are not evaluated in this study.

8.10 Immunogenicity Assessments

Immunogenicity Assessments are described in Section 8.2.

8.11 Health Economics

Health economics parameters are not evaluated in this study.

9.0 STATISTICAL CONSIDERATIONS

The Statistical Analysis Plan (SAP) will be finalized prior to first subject first visit (FSFV).

9.1 Statistical Hypotheses

The null hypotheses for vaccine-homologous HI titer at Day 43 in 18 to 64 years 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% CI for the SPR meets or exceeds 60% for adults ≥65 years of age.

9.2 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 any in the first group that is 7.5 mcg antigen + AS03A. This assumes that the SPR are 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.

9.3 Analysis Sets

Table 9 Analysis Sets

Analysis Set	Description	Analyses Evaluated
Screened	All participants who were screened for eligibility.	Study Population
Enrolled (ENR)	All participants who were randomized, received study intervention or had immunogenicity blood sample.	Study Population
Exposed Set (ES)	Participants who received a study intervention. Participants will be analyzed according to the study intervention administered at dose 1.	Safety (unsolicited AE, number of participants with changes in laboratory toxicity grading from baseline, SAE, pIMD, MAE)
Diary Set (DS)	Participants who received a study intervention and provided information on solicited AEs. Participants will be analyzed according to the study intervention administered at dose 1.	Solicited AE
Per Protocol Set (PPS)	All eligible participants who received the 2 doses of study intervention as per protocol, had Day 1 and Day 43 post dose anti-HI immunogenicity results 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 serological blood sample deviated from blood draw intervals (refer to Table 2) • Results from a serological blood sample occurred after intercurrent conditions that may interfere with immunogenicity (i.e., immunosuppressive, immunodeficient conditions, or malignancy) or after a prohibited concomitant medication/vaccination The analysis will be done according to the treatment that participants received at Visit 1.	Efficacy The PPS will be used for the immunogenicity analyses.

9.3.1 Criteria for Elimination from Analysis

All conditions leading to full or partial data elimination of a participant for the per protocol set (PPS) analysis will be classified as major protocol deviations. These conditions are already mentioned in the PPS definition and will be further detailed in the SAP and the Study Deviation Rules document which will be finalized prior to the interim analysis defined in Section 9.5.

Key major deviations include, but are not limited to, the following:

- Participants enrolled who did not meet eligibility criteria
- Participants incorrectly vaccinated
- Participants who did not receive study vaccinations as planned in protocol
- Participants who did not have serological blood draws as planned in protocol
- Participants with a blood draw outside of allowed time window
- Participants with a vaccination done outside of allowed time window. These key major deviations will be assessed based on the data collected in the eCRFs.
- Occurrence of immunosuppressive or immunodeficient conditions before a blood draw visit.

9.4 Statistical Analyses

The SAP will be developed and finalized before FSFV and will include a more technical and detailed description of the statistical analyses including the supportive analyses and demographic summaries. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1 General Considerations

All analyses will be provided separately for each age subgroup.

Derived and transformed data:

- Immunogenicity at a visit (Note: The lower limit of quantitation (LLOQ) is defined by the laboratory before the analysis and will be specified in the clinical study report).
    - A seronegative participant is a participant whose titer is below the LLOQ.
    - A seropositive participant is a participant whose titer is greater than or equal to the LLOQ.
    - Seroprotection is defined as an HI titer ≥1:40.
    - SPR is defined as the percentage of participants with an HI titer ≥1:40.
    - HI seroconversion is defined as a post-vaccination titer ≥1:40 in the serum of participants with pre-vaccination titer below 1:10 or as a ≥4-fold rise in post-vaccination HI titer with pre-vaccination titer ≥1:10.

- SCR is defined as the percentage of participants who seroconvert post-vaccination.
- MN vaccine response (VR) is defined as titer ≥4× LLOQ for participants with pre-vaccination titer below LLOQ or as a ≥4-fold increase in MN titer for participants with pre-vaccination titer ≥LLOQ.
- Vaccine response rate (VRR) is defined as the percentage of participants with vaccine response.
- Geometric Mean Titer (GMT) calculations are performed by taking the anti-log of the mean of the log concentration/titer transformations. Values for the concentrations/titers below the LLOQ will be assigned half the LLOQ for the purpose of GMT computation.
- Handling of missing data: for a given participant and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced.
- The primary and secondary HI immunogenicity analyses will be based on the PPS.
- The MN immunogenicity analyses will be based on the PPS.

- Reactogenicity and Safety − Handling of missing data: For safety analyses, participants who missed reporting symptoms (solicited or unsolicited) or concomitant medications will not be imputed. Therefore, the analysis of the solicited symptoms based on the DS will include only participants/doses with documented safety data (i.e., symptom screen/sheet completed). Further details on the handling of missing data will be described in the SAP.

9.4.2 Participants Disposition

Participant disposition will be summarized for the enrolled set across groups and for ES for each study group and overall. The summary will include the number of participants in each analysis set defined in Section 9.3, the number and percentage of participants who received any and each study vaccination, the number and percentage of participants who completed the study and/or the primary reason for withdrawal from the study, the number and percentage of participants who completed the study vaccinations and/or the primary reason for withdrawal of study vaccination.

The number and percentage of participants who were screen failures and the major reason for screen failure will be summarized for the Screened set as overall.

Major deviations will be summarized for the ES for each study group and overall.

The reason for elimination from the DS and from the PPS will also be summarized at each vaccination and post-vaccination blood draw respectively.

Listings will be provided for disposition data and deviation data based on the enrolled set.

9.4.3 Primary Endpoint(s)/Estimand(s) Analysis

9.4.3.1 Immunogenicity

Primary immunogenicity analyses will be based on the PPS.

GMTs and associated 95% CI will be calculated for each study group for vaccine-homologous H5N8 HI titer at Day 43.

GMFR increase at Day 43, compared to pre-vaccination and associated 95% CI will be calculated for each study group for vaccine-homologous H5N8 HI titer at Day 43. The GMT and GMFR CIs will be derived from an Analysis of Covariance (ANCOVA) model on log-transformed titer. The 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.

SPR at Day 43 will be calculated for each study group for vaccine-homologous H5N8 HI titer along with Clopper-Pearson exact two-sided 98.75% CIs.

9.4.3.2 Safety

The analysis of reactogenicity will be based on the DS while the analysis of other safety endpoints such as unsolicited events will be based on the ES. The following analysis will be generated for each vaccine group.

Solicited administration site and systemic endpoints

The following summaries will be generated for any grade (Table 13), grade ≥2, grade ≥3, medically attended, ongoing after day 7:

- Occurrence of at least one solicited administration site event during a 7-day follow-up period (i.e., day of vaccination and 6 subsequent days) after each vaccination and overall.
- Occurrence of at least one solicited systemic event during a 7-day follow-up period (i.e., day of vaccination and 6 subsequent days) after each vaccination and overall.
- Duration of each solicited AE starting on the day of vaccination or on one of the 6 subsequent days will be summarized after each vaccination and overall.

Frequencies and percentages of participants experiencing each event will be presented for each vaccination and across vaccinations with Clopper-Pearson exact 95% CIs.

If a solicited event occurs more than once for a participant, it will be counted in the summary only once for each level of summarization, according to the maximal severity.

Laboratory endpoints

The percentage of participants with an increase in laboratory toxicity grading 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 vaccination.

Unsolicited AE and MAE endpoints

- Occurrence of unsolicited AEs within 21 days (day of vaccination and 20 subsequent days) after each vaccination and overall.
- Occurrence of MAEs within 21 days (day of vaccination and 20 subsequent days) after each vaccination and also through 6 months post dose 2.

SAE/pIMD endpoints

- Occurrence of SAEs and pIMDs up to Visit 5 (Day 43) and also through 6 months post dose 2.

The original verbatim terms used by investigators to identify AEs in the eCRFs will be mapped to preferred terms (PTs) using the Medical Dictionary for Regulatory Activities (MedDRA). The AEs will then be grouped by Medical Dictionary for Regulatory Activities PTs into frequency tables according to system organ class.

For each of the unsolicited AE, SAE, and pIMD endpoints the number of participants and percentage will be summarized regardless of MedDRA classification and by system organ class and by preferred term within system organ class for each study group.

Separate summaries will be produced for the following categories:

- AE of any grade
- AEs of any grade that are possibly or probably related to vaccine(s)
- Grade 3 AE
- Grade 3 AE that are possibly or probably related to vaccine(s)
- MAE of any grade
- pIMDs
- SAEs
- SAEs related to vaccine
- Fatal SAE
- Fatal SAE related to vaccine

Data listings of all AEs will be provided by participant. In addition, AEs in the categories above will be provided as listed data.

9.4.4 Secondary Endpoint(s) Analysis

9.4.4.1 Immunogenicity

Secondary immunogenicity analyses will be based on the PPS.

Geometric mean titers with associated 95% CI will be calculated for each study group for vaccine-homologous H5N8 HI titer at Days 1, 22, and 6 months post dose 2. Geometric mean fold rise increase compared to pre-vaccination and associated 95% CI will be calculated at Days 22, and 6 months for each study group for vaccine-homologous H5N8 HI antibody titer. The GMT and GMFR CIs will be derived from an ANCOVA model on log-transformed titer. The 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.

The following aggregate variables will be calculated for each study group for vaccine-homologous H5N8 HI antibody titer along with Clopper-Pearson exact two-sided 95% CIs:

- SCR at Day 22, Day 43, and 6 months post dose 2, and
- SPR at Day 1, 22, and 6 months post dose 2.

For a subset of participants with Microneutralization (MN) antibody titers, the following aggregate variables will be calculated for each study group for vaccine-homologous H5N8 MN antibody titer:

- GMTs at Days 1, 22, 43, and 6 months post dose 2
- Seropositivity rates at Days 1, 22, 43, and 6 months post dose 2
- VRR at Days 22, 43, and 6 months post dose 2

The GMTs with 95% CIs will be tabulated by visit for each study group. For seropositivity/VRR, percentage of participants will be calculated with Clopper-Pearson exact two-sided 95% CIs.

9.4.5 Demography and Baseline Characteristic Analyses

Demographic characteristics (age, gender, race, center, country, ethnicity, and occupation) will be tabulated per study group for ES and PPS, as described in the SAP.

For continuous characteristics, mean, range, and standard deviation will be calculated.

For discrete variables, distribution, and associate frequency will be calculated.

Listings will be provided for demographic characteristic data based on the enrolled set.

9.5 Interim Analysis

An interim analysis will be performed on data collected through the Day 43 visit. This interim analysis will provide treatment-level unblinded summaries for GSK, and BARDA, and no individual unblinding data will be provided. The details of the interim analysis are provided in Section 9.5.1 and will be fully detailed in the SAP.

9.5.1 Sequence of Analyses

9.5.1.1 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.
- Analyses of SAEs, pIMDs, MAEs, pregnancies, and withdrawals due to AEs, collected up to the Day 43 visit.
- 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.

9.5.1.2 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.
- 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.

9.5.1.3 Final Analysis (6 Months Post Dose 2)

A final data analysis will be performed at the EOS (6 months post dose 2) of all primary and secondary endpoints based on the clean data, including evaluations of:

- Immunogenicity at all measured time points.
- Solicited administration site events and solicited systemic events data reported within 7 days after each vaccination (day of vaccination and 6 subsequent days following each vaccination).
- Unsolicited AEs reported up to the Day 43 visit (day of vaccination and 20 subsequent days after each vaccination).
- Concomitant medications reported up to the Day 43 visit.
- SAEs, pIMDs, MAEs, and withdrawals due to AEs collected throughout the entire study.
- Pregnancies throughout the entire study. An integrated clinical study report containing all data will be written and made available to the investigators.

9.5.2 Statistical Consideration for Interim Analysis

Since the primary endpoints for the study will be complete by the Day 43 visit (collection past Day 43 includes only assessments for SAEs, pIMDs, MAEs, and immunogenicity at 6 months post dose 2), no statistical consideration for multiplicity will be given to account for changes in the results reported at the interim analysis compared to the final analysis. For the primary immunogenicity analysis, which will be reported at Day 43 the overall type I error rate is fixed at 2.5% and a Bonferroni adjustment will be applied to allow simultaneous multiple comparisons of each antigen/adjuvant group leading to 0.625% nominal type I error. For the primary safety analyses no adjustment for multiple comparisons will be made in each antigen/adjuvant group.

9.6 Data Monitoring Committee

Not applicable.

10.0 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines
- Applicable ICH GCP guidelines
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, IB, Investigational Directions for Use, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs, or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the study site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

After reading the protocol, each investigator will sign the protocol signature page and send a copy of the signed page to IQVIA. The study will not start at any study site at which the investigator has not signed the protocol.

10.1.2 Adequate Resources

The investigator is responsible for supervising any individual or party to whom the investigator delegates study-related duties and functions conducted at the study site.

If the investigator/institution retains the services of any individual or party to perform study-related duties and functions, the investigator/institution should ensure this individual or party is qualified to perform those study-related duties and functions and should implement procedures to ensure the integrity of the study-related duties and functions performed and any data generated.

10.1.3 Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.4 Informed Consent Process

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or participant's caregiver(s) and answer all questions regarding the study.

Potential participants must be informed that their participation is voluntary. Participants or participant's caregiver(s) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy, and data protection requirements, where applicable, and the IRB/IEC or study site.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant or caregiver(s).

10.1.5 Recruitment Strategy

Poultry workers are at increased risk of avian influenza. It is intended to recruit from this population.

10.1.6 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study -related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between Sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches, and respective communication and co-operation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. GSK and/or trusted third parties working on behalf of GSK and/or institutions working with GSK for the purposes of this study are contractually bound to protect participant coded data. GSK will protect participant coded data and will only share it as described in the ICF.

10.1.7 Committees Structure

An iSRC will be in place for this study. This 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. If a pausing/holding rule (Section 8.4) is met, this will trigger a hold of vaccination and a review. A decision will be made, based on the review, as to whether enrollment in the study will be allowed to resume.

A SRT is in place for each GSK product. It comprises of a global cross-functional team responsible for the ongoing assessment of benefit-risk for a product. The SRT contribute to the continual assessment of incoming new efficacy and safety information.

10.1.8 Dissemination of Clinical Study Data

The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Clinical Study Register in compliance with applicable regulations/GSK policy. GSK will aim to register protocols summaries prior to study start and target results summaries submission within 12 months of primary/study completion date. Where external regulations require earlier disclosure, GSK will follow those timelines.

Where required by regulation, summaries will also be posted on applicable national or regional clinical study registers.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and provided reasonable access to statistical tables, figures, and relevant reports. GSK will also provide the investigator with the full summary of the study results, including a summary of trial results understandable to laypersons. The investigator is encouraged to share the plain language summary with the study participants, as appropriate. The full study report will be made available upon request, after the decision on marketing authorization by regulatory authorities.

GSK will provide the investigator with the randomization codes and participant-level line listings for their site only after completion of the full statistical analysis.

GSK intends to make anonymized participant-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding.

10.1.9 Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the case report form (CRF).
- Guidance on completion of eCRFs will be provided in eCRF completion guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits will be predefined in the Project Management Plan to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the quality tolerance limits and remedial actions taken will be summarized in the clinical study report.

- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years from the final clinical study report or equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.10 Source Documents

The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study site's participants. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data and its origin can be found in Monitoring Management Plan.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized study site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is

being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.11 Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first study site open.

Study/Site Termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development.

For study site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.12 Publication Policy

The results of this study may be published in peer reviewed scientific literature and/or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results in accordance with standard editorial and ethical practice and as per the Sponsor's internal policy. Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors (ICMJE) authorship requirements.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multi-center studies only in their entirety and not as individual study site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Where required by regulation, the names of the sponsor signatory and investigator signatory will be made public.

GSK intends to make anonymized participant-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding. Data will be shared with researchers in a non-identifying way, and appropriate measures will be taken to protect PI; these measures will comply with data protection and privacy laws that apply.

10.2 Appendix 2: Clinical Laboratory Tests

Hemagglutination Inhibition Assay

Hemagglutination inhibition titers are determined using the method derived from the WHO Manual on Animal Influenza Diagnosis and Surveillance, WHO/CDS/CSR/NCS/2002.5.

Measurements are conducted on thawed frozen serum samples with a standardized and comprehensively validated micromethod. The standard operating procedure describes a HI test for detecting H5N8 influenza A specific responses, such as those following influenza virus vaccinations. Briefly, serum samples are first adsorbed with RBCs to remove non-specific agglutinins and then treated with receptor destroying enzyme overnight to remove non-specific inhibitors of the hemagglutination, then diluted to 1:10, and serial diluted 2-fold in duplicate from 1:10 to 1:10240. After addition of an equal volume of standardized virus (4 HAU/25 µL), antibodies that inhibit virus-mediated hemagglutination react with the virus for 1 hour at room temperature, and then horse red blood cells (RBCs) are added to the mixture. Plates are tilted and the titer is the reciprocal of the last dilution that fully inhibits hemagglutination as compared to a red blood cell control well. Each serum sample will be tested in duplicate within the same assay. The final result corresponds to the GMT for the duplicate.

Microneutralization Assay

Microneutralization titers are determined using the method derived from the WHO Manual for the laboratory diagnosis and virological surveillance of influenza.[21]
Measurements are conducted on thawed frozen serum samples. Samples are heat-inactivated at 56°C. A standardized amount of virus is mixed with serial dilutions of serum and incubated at 37°C to allow binding of the antibodies to the virus. A cell suspension containing a defined amount of Madin-Darby Canine Kidney cells is then added to the mixture of virus and antiserum and incubated at 37°C. After overnight incubation, plates are fixed and the amount of virus per well is detected by enzyme-linked immunosorbent assay using anti-nucleoprotein monoclonal antibodies. The virus neutralizing titer is determined using a formula that calculates the midpoint optical density of uninfected cells and virus infected (without neutralization) cells.

10.3 Appendix 3: FDA Toxicity Grading Scale

The laboratory values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.[22]

Table 10 Table of Laboratory Abnormalities

Serum *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)****
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0

Serum *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)****
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000

Abbreviations: ALT=alanine aminotransferase; AST=aspartate transaminase; BUN=blood urea nitrogen; ULN=upper limit of normal; WBC=white blood cell.

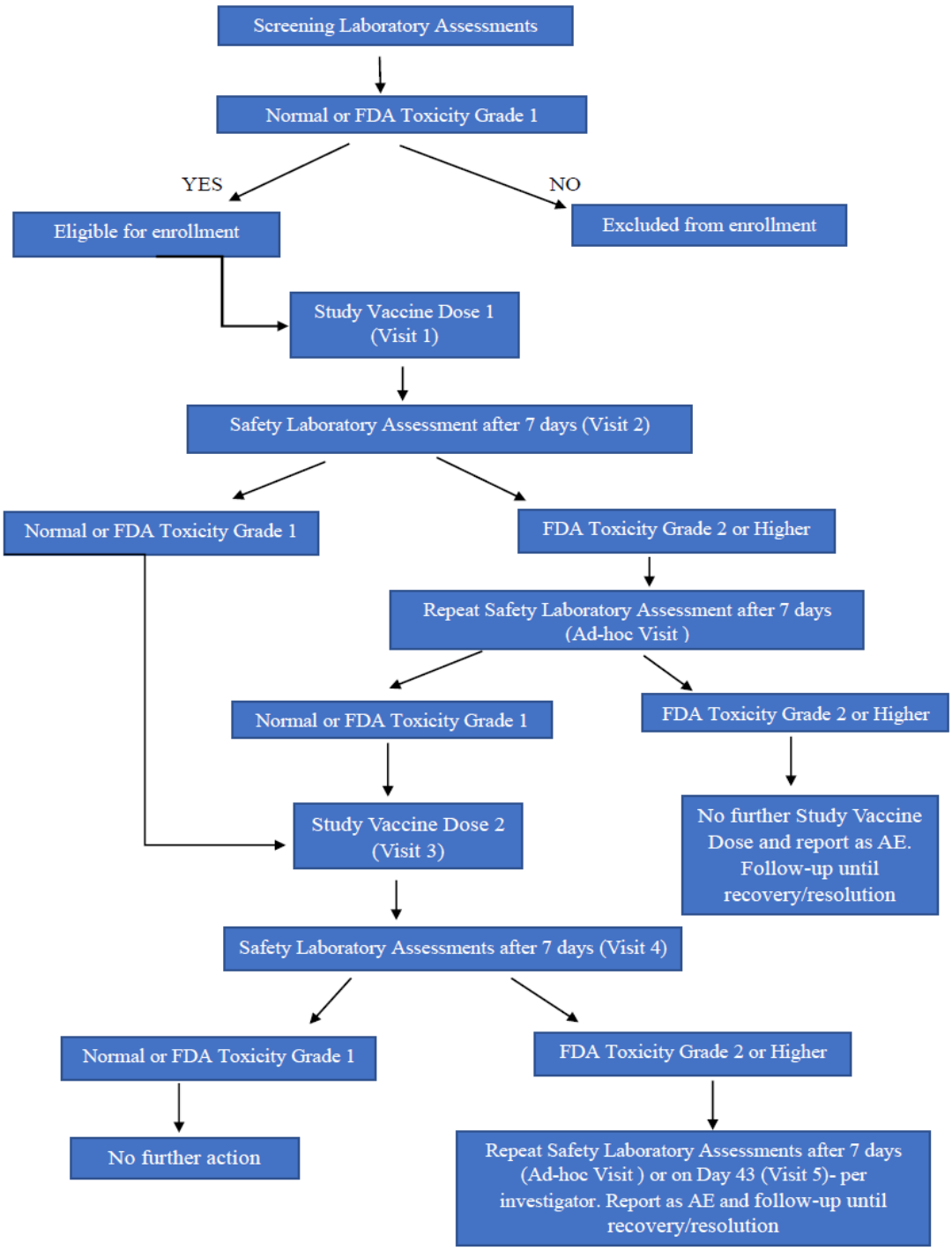
* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a Grade 3 parameter (125-129 mE/L) should be recorded as a Grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

Source: Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.[22]

10.4 Appendix 4: Management of Participants with Abnormal Laboratory Values

Figure 2 Screening and Safety Laboratory Schema



10.5 Appendix 5: AEs, SAEs, and pIMDs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting for Study Intervention

10.5.1 Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention.

  NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Definition of Unsolicited AEs, MAEs, and Solicited Events

- An unsolicited AE is an AE that was not otherwise solicited in a participant diary and that is communicated by a participant/participant's caregiver(s) who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs.
- An unsolicited AE is an AE that was either not included in the list of solicited events or could be included in the list of solicited events but with an onset outside the specified period of follow-up for solicited events. Unsolicited AEs must have been communicated by [participants/ participant's caregiver(s)] who has signed the informed consent. Unsolicited AEs include both serious and non-serious AEs.
- Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The participant/participant's caregiver(s) will be instructed to contact the study site as soon as possible to report MAEs, as well as any events that, though not medically attended, are of participant/participant's caregiver(s) concern. Detailed information about reported unsolicited AEs will be collected by qualified study site personnel and documented in the participant's records.
- Unsolicited AEs that are not medically attended nor perceived as a concern by the participant/participant's caregiver(s) will be collected during an interview with the participant/participant's caregiver(s) and by review of available medical records at the next visit.
- Solicited events are predefined administration site and systemic events for which the participant is specifically questioned, and which are noted by the participant in their diary.
- Solicited Administration Site Events

Table 11 Solicited Administration Site Events

All Age Subgroups
Pain

Redness
Swelling

- Solicited Systemic Events

Table 12 Solicited Systemic Events

All Age Subgroups
Fatigue
Fever
Headache
Muscle Ache
Joint pain
Shivering (Chills)
Sweating
Gastrointestinal symptoms: Nausea Vomiting Diarrhea Abdominal pain

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

- Significant failure of an expected pharmacologic or biological action.
- Events that occur as a result of protocol-mandated procedures (i.e., invasive procedures, modification of participant's previous therapeutic regimen).

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital, admission for routine examination.).
- Anticipated day-to-day- fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. Pre-existing diseases will be recorded in the medical history section of the eCRF.
- Hospitalization for elective treatment of a pre-existing condition (known or diagnosed before signing the informed consent) that did not worsen from baseline.

10.5.2 Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a. Results in death

- For SAEs with the outcome of death, the date and cause of death will be recorded on the appropriate CRF.

b. Is life-threatening

- The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment

that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

- The term congenital anomaly/birth defect means there is suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.

f. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy).

g. Is a suspected transmission of any infectious agent via an authorized medicinal product.

h. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

10.5.3 Recording and Follow-Up of AE, SAE, and/or pIMD

AE, SAE, and pIMD Recording

- When an AE/SAE/pIMD occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/pIMD information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor or designee in lieu of completion of the applicable/required report form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor or designee. In this case, all participant identifiers, with the exception of the

participant number, will be redacted on the copies of the medical records before submission to the Sponsor or designee.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

10.5.3.1 Assessment of Intensity and Causality

Assessment of Intensity

The intensity of the following solicited AEs will be assessed as described:

Table 13 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.
	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
Swelling at administration site		Record greatest surface diameter in mm
Temperature		Record temperature in °C/°F. Oral route is preferred.

The maximum intensity of local injection site redness/swelling will be scored as follows:

0: ≤20 mm

1: >20 to 50 mm

2: >50 to 100 mm

3: >100 mm

The maximum intensity of fever will be scored as follows:

0: <38.0°C (<100.4°F)

1: ≥38.0 – 38.4°C (≥100.4 – 101.2°F)

2: ≥38.5 – 38.9°C (≥101.3 – 102.1°F)

3: ≥39.0 – 40.0°C (≥102.2 – 104.0°F)

4: >40.0°C (>104.0°F)

The investigator will assess the maximum intensity that occurred over the duration of the event for all unsolicited AEs (including SAEs) recorded during the study. The assessment will be based on

the investigator's clinical judgement.

The following definitions are to be used to rate the severity of an AE:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

An AE that is assessed as Grade 3 (severe) should not be confused with an SAE. Grade 3 is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets 1 of the predefined outcomes as described in the Section 10.5.2.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/pIMD. The investigator will use clinical judgment to determine the relationship.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- For causality assessments, events assessed as having a reasonable possibility of being related to study intervention will be considered "related." Events assessed as having no reasonable possibility of being related to study intervention will be considered "unrelated."
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE/pIMD, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/pIMD and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor or designee. However, it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor or designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Causality should be assessed by the investigator using the following question:

Is there a reasonable possibility that the unsolicited AE may have been caused by the study vaccine/product?

YES	:	There is a reasonable possibility that the study vaccine/product contributed to the AE.
NO	:	There is no reasonable possibility that the AE is causally related to the administration of the study vaccine/product. There are other, more likely causes and administration of the study vaccine/product is not suspected to have contributed to the AE.

If an event meets the criteria to be determined as 'serious' (see Section 10.5.2), additional examinations/tests will be performed by the investigator to determine ALL possible contributing factors for each SAE.

Possible contributing factors include:

- Medical history.
- Other medication.
- Protocol required procedure.
- Other procedure not required by the protocol.
- Erroneous administration.
- Other cause (specify).

Assessment of Outcomes

The investigator will assess the outcome of all serious and non-serious unsolicited AEs recorded during the study as:

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered with sequelae/resolved with sequelae
- Fatal (SAEs only).

Follow-up of AEs, SAEs, or pIMDs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or designee to elucidate the nature and/or causality of the AE, SAE, or pIMD as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the Sponsor or designee with a copy of any postmortem findings including histopathology.

- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE and/or pIMD data to the Sponsor or designee within 24 hours of the investigator's awareness of the information.
- After the initial AE/SAE/pIMD/pregnancy or any other event of interest, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs will be followed until the event is resolved, subsided, stabilized, disappeared, otherwise explained, or the participant is lost to follow-up, irrespective of seriousness or relatedness.

Follow-up during the study

- AEs/pIMDs documented at a previous visit/contact and defined as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until resolved, subsided, stabilized, disappeared, otherwise explained, or the participant is lost to follow-up.
- If a participant dies during their participation in the study or during a recognized follow-up period, GSK will be provided with any available postmortem findings, including histopathology.

Follow-up of pregnancies

- Pregnant participants will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK using the electronic pregnancy report and the AE Report if applicable. Generally, the follow-up period does not need to be longer than 6 to 8 weeks after the estimated date of delivery.
- Regardless of the reporting period for SAEs in this study, if the pregnancy outcome is an SAE, it should always be reported as such.
- Furthermore, the investigator must report any SAE occurring as a result of a post-study pregnancy that is considered by the investigator to be reasonably related to the study intervention, to GSK as described in the Section 10.5.4.

10.5.4 Updating of SAE, pIMD, and Pregnancy Information after Removal of Write Access to the Participant's eCRF

Updating SAEs, pIMDs, and/or pregnancies after removal of write access to participant's eCRF
• When additional SAE, pIMD, or pregnancy information is received after write access to the participant's eCRF is removed, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be sent to the Sponsor or designee.

10.5.5 Reporting of SAEs

SAE Reporting to the Sponsor or Designee via an Electronic Data Collection System
• The primary mechanism for reporting an SAE to the Sponsor or designee will be the electronic data collection system. The study site will enter the event into the electronic data collection system within 24 hours of the investigator's awareness of the event.

- If the electronic system is unavailable, then the study site will use the paper SAE report form (see next section) to report the event and will enter the event into the electronic data collection system as soon as the system becomes available.
- After the study is completed at a given study site, the electronic data collection system will be taken offline to prevent the entry of new data or changes to existing data.
- If a study site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection system has been taken offline, then the study site can report this information on a paper SAE report form (see next section) to the Sponsor or designee.
- If the site during the course of the study or post-study becomes aware of any serious, non-serious AEs, pregnancy exposure, related to any GSK non-IMP they will report these events to GSK or to the concerned competent authority via the national spontaneous reporting system. These will be classified as spontaneous individual case safety reports.
- Contacts for SAE reporting can be found in study materials.

SAE Reporting to the Sponsor or Designee via Paper SAE Report Form

- The back-up mechanism for reporting an SAE to the Sponsor or designee will be the paper SAE report form. The study site will submit the SAE report form, via email, within 24 hours of the investigator's awareness of the event. Facsimile transmission may be utilized as an alternative mode of submission, if necessary.
- Notification of SAE information via telephone does not replace the need for the investigator to complete, sign and submit the paper SAE report form to the Sponsor or designee within 24 hours of the investigator's awareness of the event.
- Contacts for SAE reporting can be found in study materials.

10.6 Appendix 6: Contraceptive and Barrier Guidance and Collection of Pregnancy Information

10.6.1 Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the Following Categories Are Not Considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
    a) Documented hysterectomy.
    b) Documented bilateral salpingectomy.
    c) Documented bilateral oophorectomy.

For permanently sterile individuals due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry. If reproductive status is questionable, additional evaluation should be considered.

NOTE: Documentation can come from the study site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female:
    a) A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    b) Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.6.2 Contraception Guidance

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table below. Female participants of childbearing potential should have practiced effective contraception methods as described below for 2 months prior to the first dose of the study vaccine, through 2 months after the second dose of the study vaccine.

Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation • Oral. • Intravaginal. • Transdermal.
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral. • Injectable.
Highly Effective Methods That Are User Independent[a]
• Implantable progestogen only hormonal contraception associated with inhibition of ovulation • Intrauterine device. • Intrauterine hormone-releasing system. • Bilateral procedural tubal occlusion, such as ligation.
Vasectomized partner *A vasectomized partner is a highly effective birth control method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

Pregnancy Testing:

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine pregnancy test.
- Additional pregnancy testing at times specified in the SoA (Section 1.3) during the treatment period.

Collection of Pregnancy Information

Female Participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the

appropriate form and submitted to the Sponsor or designee within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor or designee. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication will be reported as an AE or SAE. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus, stillbirth, or neonatal death]), the investigator will report according to the SAE reporting procedures described in Section 10.5.
- Any post-study pregnancy-related SAE considered reasonably related to the study treatment by the investigator will be reported to the Sponsor or designee as described in Section 10.5.3. While the investigator is not obligated to actively seek this information in former participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant after the first study intervention dose must not receive the second dose of the study intervention but may continue other study procedures at the discretion of the investigator.

10.7 Appendix 7: Abbreviations and Glossary of Terms

Table 14 Abbreviations

Abbreviation	Definition
AE	Adverse event
AESI	Adverse Events of Special Interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
BARDA	Biomedical Advanced Research and Development Authority
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRF	Case report form
CTR	Clinical Trial Regulation
CVV	Candidate Vaccine Virus
eCRF	Electronic case report form
DS	Diary set
EOS	End of study
ES	Exposed set
EU	European Union
FDA	Food and Drug Administration
FSFV	First subject first visit
FSH	Follicle-stimulating Hormone
GCP	Good Clinical Practice
GMFR	Geometric Mean Fold Rise
GMT	Geometric Mean Titer
GSK	GlaxoSmithKline
H5N8	Monovalent Influenza A/Astrakhan/3212/2020-like virus
HA	Hemagglutinin
HI	Hemagglutination Inhibition
HRT	Hormone replacement therapy

Abbreviation	Definition
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
iSRC	Internal safety review committee
IRB	Institutional Review Board
IWRS	Interactive Voice/Web Response System
LAR	Legally authorized representative
LL	Lower limit
LLOQ	Lower limit of quantitation
LSLV	Last subject last visit
MAE	Medically Attended Adverse Events
MedDRA	Medical Dictionary for Regulatory Activities
MN	Microneutralization
PI	Principal Investigator
pIMD	Potential Immune-Mediated Disease
PPS	Per protocol set
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SC	Seroconversion
SCR	Seroconversion Rate
SoA	Schedule of Activities
SP	Seroprotection
SPR	Seroprotection Rate
SRT	Safety Review Team
TC	Telephone Contact
US	United States
VR	Vaccine Response

Abbreviation	Definition
VRR	Vaccine Response Rate
WOCBP	Women of Childbearing Potential

Table 15 Glossary of Terms

Adverse event:	Any untoward medical occurrence in a patient or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.
Blinding:	A procedure in which 1 or more parties to the trial are kept unaware of the intervention assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious AEs In an open-label study, no blind is used. Both the investigator and the participant know the identity of the intervention assigned.
Caregiver:	A 'caregiver' is a person who has a continuous caring role for a participant or may be a person having substantial periods of contact with a participant and/or is engaged in his/her daily health care (e.g., a relative of the participant including family members or friends). In the context of this study, a caregiver can be appointed by the participant to oversee and support the participant's compliance with protocol-specific procedures (such as transcribing responses to diaries, receiving phone calls, planning study visits, etc.). However, at no time, the caregiver should evaluate the participant's health status while answering diaries or make decisions on behalf of the participant.
Eligible:	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.

Enrolled participant:	'Enrolled' means a participant's agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. Refer to the Section 9.3 of the protocol for the definition of 'enrolled set' applicable to the study.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per protocol analysis.
Immunological correlate of protection:	A correlate of risk that has been validated to predict a certain level of protection from the targeted endpoint.
Intercurrent medical condition:	A condition that has the capability of altering the immune response to the study vaccine or is confirmed to have an alteration of the participant's initial immune status.
Intervention number:	A number identifying an intervention to a participant, according to intervention allocation.
Intervention:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a participant.
Investigator:	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the Principal Investigator. The investigator can delegate trial-related duties and functions conducted at the trial site to qualified individual or party to perform those trial-related duties and functions.
Participant number:	A unique identification number assigned to each participant who consents to participate in the study.
Participant:	Term used throughout the protocol to denote an individual who has been contacted to participate or who participates in the clinical study as a recipient of the study intervention (vaccine(s)/product(s)/control). Synonym: subject.
Protocol amendment:	The International Council on Harmonisation (ICH) defines a protocol amendment as: 'A written description of a

	change(s) to or formal clarification of a protocol.' GSK further details this to include a change to an approved protocol that affects the safety of participants, scope of the investigation, study design, or scientific integrity of the study.
Randomization:	Process of random attribution of intervention to participants to reduce selection bias.
Site Monitor:	An individual assigned by the Sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.
Solicited event:	Events to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the participant or an observer during a specified follow-up period following study intervention administration.
Source data:	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).
Source documents:	Original legible documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, laboratories and at medico-technical departments involved in the clinical trial).
Study intervention:	Any investigational or marketed product(s) or placebo intended to be administered to a participant during the study.
Unsolicited adverse event:	Any AE reported in addition to those solicited during the clinical study. Also, any 'solicited' symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.

10.8 Appendix 8: List of Potential Immune-Mediated Diseases

The GSK list of pIMDs is based on MedDRA version 26.1.

Table 16 GSK List of pIMD MedDRA Terms

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

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

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

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

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

MedDRA Term Name	Term Level
Hypersensitivity vasculitis	PT
Hypoglossal nerve paralysis	PT
Hypoglossal nerve paresis	PT
Idiopathic inflammatory myopathy	PT
Idiopathic interstitial pneumonia	PT
Idiopathic pulmonary fibrosis	PT
IgA nephropathy	PT
IgM nephropathy	PT
IIIrd nerve paralysis	PT
IIIrd nerve paresis	PT
Immune effector cell-associated HLH-like syndrome	PT
Immune thrombocytopenia	PT
Immune-complex membranoproliferative glomerulonephritis	PT
Immune-mediated adrenal insufficiency	PT
Immune-mediated adverse reaction	PT
Immune-mediated arthritis	PT
Immune-mediated cholangitis	PT
Immune-mediated cholestasis	PT
Immune-mediated cystitis	PT
Immune-mediated cytopenia	PT
Immune-mediated dermatitis	PT
Immune-mediated encephalitis	PT
Immune-mediated encephalopathy	PT
Immune-mediated endocrinopathy	PT
Immune-mediated enterocolitis	PT
Immune-mediated gastritis	PT
Immune-mediated hepatic disorder	PT
Immune-mediated hepatitis	PT
Immune-mediated hyperthyroidism	PT
Immune-mediated hypophysitis	PT
Immune-mediated hypothyroidism	PT
Immune-mediated lung disease	PT
Immune-mediated myasthenia gravis	PT

MedDRA Term Name	Term Level
Immune-mediated myelitis	PT
Immune-mediated myocarditis	PT
Immune-mediated myositis	PT
Immune-mediated nephritis	PT
Immune-mediated neurological disorder	PT
Immune-mediated neuropathy	PT
Immune-mediated oesophagitis	PT
Immune-mediated optic neuritis	PT
Immune-mediated pancreatitis	PT
Immune-mediated pancytopenia	PT
Immune-mediated pericarditis	PT
Immune-mediated polyserositis	PT
Immune-mediated renal disorder	PT
Immune-mediated scleritis	PT
Immune-mediated thyroiditis	PT
Immune-mediated uveitis	PT
Immune-mediated vasculitis	PT
Immunoglobulin G4 related disease	PT
Inclusion body myositis	PT
Inflammatory bowel disease	PT
Injection site vasculitis	PT
Insulin autoimmune syndrome	PT
Interstitial granulomatous dermatitis	PT
Interstitial lung disease	PT
Intramyelinic oedema	PT
IVth nerve paralysis	PT
IVth nerve paresis	PT
Juvenile idiopathic arthritis	PT
Juvenile polymyositis	PT
Juvenile psoriatic arthritis	PT
Juvenile spondyloarthritis	PT
Kawasaki's disease	PT
Keratoderma blenorrhagica	PT

MedDRA Term Name	Term Level
Langerhans' cell histiocytosis	PT
Laryngeal rheumatoid arthritis	PT
Latent autoimmune diabetes in adults	PT
Leukoencephalomyelitis	PT
Leukoencephalopathy	PT
Lewis-Sumner syndrome	PT
Lichen planopilaris	PT
Lichen planus	PT
Lichen planus pemphigoides	PT
Linear IgA disease	PT
Liver sarcoidosis	PT
Loefgren syndrome	PT
Lumbosacral radiculoplexus neuropathy	PT
Lupoid hepatic cirrhosis	PT
Lupus anticoagulant hypoprothrombinaemia syndrome	PT
Lupus cystitis	PT
Lupus encephalitis	PT
Lupus endocarditis	PT
Lupus enteritis	PT
Lupus hepatitis	PT
Lupus myocarditis	PT
Lupus myositis	PT
Lupus nephritis	PT
Lupus pancreatitis	PT
Lupus pleurisy	PT
Lupus pneumonitis	PT
Lupus vasculitis	PT
Lupus-like syndrome	PT
Lymphocytic hypophysitis	PT
MAGIC syndrome	PT
Marburg's variant multiple sclerosis	PT
Marine Lenhart syndrome	PT
Melkersson-Rosenthal syndrome	PT

MedDRA Term Name	Term Level
Membranous-like glomerulopathy with masked IgG-kappa deposits	PT
Mesangioproliferative glomerulonephritis	PT
Metastatic cutaneous Crohn's disease	PT
Microscopic enteritis	PT
Microscopic polyangiitis	PT
Miller Fisher syndrome	PT
Mixed connective tissue disease	PT
Mononeuritis	PT
Mononeuropathy multiplex	PT
Morphoea	PT
Morvan syndrome	PT
Mucous membrane pemphigoid	PT
Multifocal motor neuropathy	PT
Multiple sclerosis	PT
Multiple sclerosis pseudo relapse	PT
Multiple sclerosis relapse	PT
Multiple sclerosis relapse prophylaxis	PT
Multisystem inflammatory syndrome	PT
Multisystem inflammatory syndrome in adults	PT
Multisystem inflammatory syndrome in children	PT
Muscular sarcoidosis	PT
Myasthenia gravis	PT
Myasthenia gravis crisis	PT
Myasthenic syndrome	PT
Myelin oligodendrocyte glycoprotein antibody-associated disease	PT
Myelitis	PT
Myelitis transverse	PT
Myocarditis	PT
Myopericarditis	PT
Narcolepsy	PT
Neuralgic amyotrophy	PT
Neuritis	PT
Neuritis cranial	PT

MedDRA Term Name	Term Level
Neuromyelitis optica pseudo relapse	PT
Neuromyelitis optica spectrum disorder	PT
Neuropsychiatric lupus	PT
Neurosarcoidosis	PT
Nodular vasculitis	PT
Noninfectious myelitis	PT
Noninfective encephalitis	PT
Noninfective encephalomyelitis	PT
Noninfective oophoritis	PT
Ocular myasthenia	PT
Ocular pemphigoid	PT
Ocular sarcoidosis	PT
Ocular vasculitis	PT
Oculofacial paralysis	PT
Olfactory nerve disorder	PT
Optic ischaemic neuropathy	PT
Optic neuritis	PT
Optic neuropathy	PT
Optic perineuritis	PT
Orexin deficiency	PT
Overlap syndrome	PT
Palindromic rheumatism	PT
Palisaded neutrophilic granulomatous dermatitis	PT
Palpable purpura	PT
Panencephalitis	PT
Paresis cranial nerve	PT
Pemphigoid	PT
Pemphigus	PT
Pericarditis	PT
Pericarditis lupus	PT
Pericarditis rheumatic	PT
Peripheral spondyloarthritis	PT
Peritonitis lupus	PT

MedDRA Term Name	Term Level
Pernicious anaemia	PT
Pleuroparenchymal fibroelastosis	PT
Polyarteritis nodosa	PT
Polychondritis	PT
Polyglandular autoimmune syndrome type I	PT
Polyglandular autoimmune syndrome type II	PT
Polyglandular autoimmune syndrome type III	PT
Polymyalgia rheumatica	PT
Polymyositis	PT
Polyneuropathy idiopathic progressive	PT
Primary biliary cholangitis	PT
Primary progressive multiple sclerosis	PT
Proctitis ulcerative	PT
Progressive facial hemiatrophy	PT
Progressive multiple sclerosis	PT
Progressive relapsing multiple sclerosis	PT
Psoriasis	PT
Psoriatic arthropathy	PT
Pulmonary fibrosis	PT
Pulmonary renal syndrome	PT
Pulmonary sarcoidosis	PT
Pulmonary vasculitis	PT
Pyoderma gangrenosum	PT
Pyostomatitis vegetans	PT
Radiculitis brachial	PT
Radiologically isolated syndrome	PT
Rasmussen encephalitis	PT
Raynaud's phenomenon	PT
Relapsing multiple sclerosis	PT
Relapsing-remitting multiple sclerosis	PT
Renal arteritis	PT
Renal vasculitis	PT
Retinal occlusive vasculitis	PT

MedDRA Term Name	Term Level
Retinal vasculitis	PT
Reynold's syndrome	PT
Rheumatic brain disease	PT
Rheumatic disorder	PT
Rheumatoid arthritis	PT
Rheumatoid arthritis-associated interstitial lung disease	PT
Rheumatoid bursitis	PT
Rheumatoid lung	PT
Rheumatoid meningitis	PT
Rheumatoid neutrophilic dermatosis	PT
Rheumatoid nodule	PT
Rheumatoid pleuritis	PT
Rheumatoid scleritis	PT
Rheumatoid vasculitis	PT
Rhupus syndrome	PT
Sarcoidosis	PT
Sarcoidosis of lymph node	PT
Satoyoshi syndrome	PT
Sclerodactylia	PT
Scleroderma	PT
Scleroderma associated digital ulcer	PT
Scleroderma renal crisis	PT
Secondary progressive multiple sclerosis	PT
Segmented hyalinising vasculitis	PT
Shrinking lung syndrome	PT
Silent thyroiditis	PT
Sjogren's syndrome	PT
SJS-TEN overlap	PT
SLE arthritis	PT
Spondylitis	PT
Spondyloarthropathy	PT
Stevens-Johnson syndrome	PT
Still's disease	PT

MedDRA Term Name	Term Level
Stoma site vasculitis	PT
Subacute cutaneous lupus erythematosus	PT
Subacute inflammatory demyelinating polyneuropathy	PT
Susac's syndrome	PT
Sympathetic ophthalmia	PT
Systemic lupus erythematosus	PT
Systemic lupus erythematosus disease activity index abnormal	PT
Systemic lupus erythematosus disease activity index decreased	PT
Systemic lupus erythematosus disease activity index increased	PT
Systemic lupus erythematosus rash	PT
Systemic scleroderma	PT
Systemic sclerosis pulmonary	PT
Takayasu's arteritis	PT
Terminal ileitis	PT
Testicular autoimmunity	PT
Thromboangiitis obliterans	PT
Thrombocytopenic purpura	PT
Thrombosis with thrombocytopenia syndrome	PT
Thrombotic thrombocytopenic purpura	PT
Tongue paralysis	PT
Toxic epidermal necrolysis	PT
Trigeminal nerve paresis	PT
Trigeminal palsy	PT
Tubulointerstitial nephritis and uveitis syndrome	PT
Tumefactive multiple sclerosis	PT
Type 1 diabetes mellitus	PT
Uhthoff's phenomenon	PT
Ulcerative keratitis	PT
Undifferentiated connective tissue disease	PT
Undifferentiated spondyloarthritis	PT
Urticarial vasculitis	PT
Uveitis	PT
Vaccination site vasculitis	PT

MedDRA Term Name	Term Level
Vagus nerve paralysis	PT
Vascular purpura	PT
Vasculitic rash	PT
Vasculitic ulcer	PT
Vasculitis	PT
Vasculitis gastrointestinal	PT
Vasculitis necrotising	PT
VIth nerve paralysis	PT
VIth nerve paresis	PT
Vitiligo	PT
Vocal cord paralysis	PT
Vocal cord paresis	PT
Vogt-Koyanagi-Harada disease	PT
Warm autoimmune haemolytic anaemia	PT
XIth nerve paralysis	PT

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

10.9 Appendix 9: Protocol and Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents.

Amendment 1.0: 23 June 2023

Overall Rationale for the Amendment 1.0:

This protocol has been amended to extend the collection of medically attended adverse events (MAEs) and to include a 30-minute observation period after each vaccination as required by the US Food and Drug Administration (FDA).

Added text in ***bold italic***, deleted text in ~~strikethrough~~.

Section # and Name	Description of Change from Original Protocol to Amendment 1.0	Brief Rationale
1.1 Synopsis, 1.2 Study Design, 1.3 Schedule of Activities, 3.0 Objectives and Endpoints, 8.5.1 Time Period and Frequency for Collecting AE, SAE, pIMD Information, 9.4.3.2 Safety, 9.5.1.1 Interim Analysis at Day 43, 9.5.1.2 Final Analysis (6 Months Post Dose 2)	Extended collection of MAEs to Visit 6/EOS (6 months post dose 2)	FDA requirement
1.3 Schedule of Activities	Added Time Point task to Table 1: ***30-minute observation period after each vaccine administration.*** Deleted collection of diary card at Visit 6/EOS	FDA requirement Diary cards are returned at Visit 5 (Day 43)
8.3.6 Post-Vaccination Observation Period	Section added	FDA requirement
8.5.2 Method of Detecting AEs and SAEs	Added text: ***Participants must be made aware of the requirement to report any new medical condition or worsening of any pre-existing medical condition requiring contact with a healthcare professional to the site staff.***	FDA requirement

Section # and Name	Description of Change from Original Protocol to Amendment 1.0	Brief Rationale
Global document update	Version control including version number and summary of changes were added to this document and minor edits have been made for clarity.	Version control, minor clarifications

Amendment 2.0: 22 August 2023

Overall Rationale for the Amendment 2.0:

This protocol has been amended to replace the table titled 'List of potential Immune-Mediated Diseases (pIMDs)' with an entire listing of pIMD terms, based on the GSK MedDRA query listing, as requested by the US Food and Drug Administration (FDA).

Added text in ***bold italic***, deleted text in ~~strikethrough~~.

Section # and Name	Description of Changes from Amendment 1.0 to Amendment 2.0	Brief Rationale
8.5.7.1 Potential Immune-Mediated Diseases	Moved pIMD table to Appendix 8	To improve flow and readability as the pIMD table length has increased.
9.3 Analysis Sets	Updated text in Table 9 Analysis Sets: • Results from a serological blood sample occurred after intercurrent conditions that may interfere with immunogenicity (i.e., immunosuppressive, ~~or~~ immunodeficient conditions***, or malignancy***) or after a prohibited concomitant medication/vaccination	To improve clarity for investigator.
9.4.5 Demography and Baseline Characteristic Analysis	Edited text: Demographic characteristics (age, gender, race, center, country, ethnicity, and occupation) will be tabulated per study group for ~~each analysis set~~ ***ES and PPS***, as described in the SAP.	Clarification
10.1.7 Committees Structure	***A SRT is in place for each GSK product. It comprises of a global cross-functional team responsible for the ongoing assessment of benefit-risk for a product. The SRT contribute to the continual assessment of incoming new efficacy and safety information.***	Added GSK SRT template text.
10.5.3.1 Assessment of Intensity and Causality	Deleted text in possible contributing factor for SAE: ~~Lack of efficacy of the vaccine/product, if applicable~~	Removed text as efficacy assessment is not a primary objective.
10.6.2 Contraception Guidance Highly Effective Contraceptive Methods That Are User Dependent	Updated text: Bilateral ***procedural*** tubal occlusion***, such as ligation***	Clarification

Section # and Name	Description of Changes from Amendment 1.0 to Amendment 2.0	Brief Rationale
	Deleted footnote and corresponding superscript 'b': ~~[b] Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the treatment period and for at least 2 months after the last dose of study intervention.~~	The AS03 adjuvanted pandemic influenza vaccines have not been associated with reduced efficacy of hormonal contraception.
10.8 Appendix 8: List of Potential Immune-Medicated Disease	Added ***Appendix 8*** and ***Table 16 GSK List of pIMDs MedDRA Terms***	To meet FDA request.
10.9 Appendix 9: Protocol and Amendment History	Added ***Appendix 9***	Version control
Global document updates	Updated cross links and references to the pIMD table Version and summary of changes were revised	Version control

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Signature of Investigator

PROTOCOL TITLE: 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, given as a two-dose series to adults 18 to 64 years of age and 65 years of age and older.

PROTOCOL NO: 219833

VERSION: Protocol Amendment 3.0

This protocol is a confidential communication of GSK. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

Instructions to the investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the study center in which the study will be conducted. Return the signed copy to IQVIA.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

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