Statistical Analysis Plan

Study ID: 209671

Official Title of Study: A Phase I/II, Observer-Blind, Randomized, Placebo-Controlled, Multi-Center Trial to Evaluate the Safety and Immunogenicity of Different Formulations of Monovalent Influenza A/Hong Kong/125/2017-like (H7N9) 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

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GlaxoSmithKline Biologicals

209671 (FLU Q-PAN H7N9=AS03-002)

A Phase I/II, Observer-Blind, Randomized, Placebo-Controlled, Multi-Center Trial to Evaluate the Safety and Immunogenicity of Different Formulations of Monovalent Influenza A/Hong Kong/125/2017-like (H7N9) 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

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Version 2.0

Prepared by: PPD, PPD

Version	Detail of Change
1.0	Original final version.
1.1	New draft version updated according to protocol amendment 2
1.2	New draft version updated according to GSK comments for v1.1
1.3	New draft version updated according to GSK comments for v1.2
1.4	New draft version updated according to GSK comments for v1.3
1.5	New draft version to address the modifications included in the final Protocol amendment 2
1.6	New draft version updated according to GSK comments for v1.5
1.7	New draft version updated according to GSK comments for v1.6
1.8	New draft version updated according to GSK comments for v1.7
2.0	New final version

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List of Abbreviations

AE	Adverse event
AESI	Adverse events of special interest
AS03	Adjuvant System 03
BMI	Body mass index
CBER	Center for Biologics Evaluation and Research
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CSR	Clinical Study Report
DIL	dilution
eCRF	Electronic case report form
FASx	Full Analysis Set (x = 1, 2)
FDA	Food and Drug Administration
GMT	Geometric mean titer
GSD	Geometric standard deviation
GSK	GlaxoSmithKline
GSKDrug	GSK Drug Dictionary
H7N9	Monovalent Influenza A/Hong Kong/125/2017-like H7N9
HA	Hemagglutinin
HI	Hemagglutination inhibition
IRT	Interactive response technology
iSRC	Internal Safety Review Committee
LL	Lower Limit
MAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MGI	Mean Geometric Increase
MN	Microneutralization
MNPPSx	Microneutralization Per Protocol Set x (x=1, 2)
MNmPPSx	Microneutralization modified Per Protocol Set x (x=1, 2)
mPPSx	Modified per protocol set x (x = 1, 2)
NC	Not calculated
pDiary	Paper diary
pIMD	Potential Immune-Mediated Disease
PPSx	Per Protocol Set x (x = 1, 2)
SAE	Serious adverse event
SCR	Seroconversion rate
SD	Standard deviation
SPR	Seroprotection rate
TLFs	Table, Listings, Figures
ToC	Table of Contents
US	United States
VRR	Vaccine response rate
WHO	World Health Organization

1 Introduction

Novel influenza A viruses, including subtypes H5N1, H3N2v, H9N2, A(H1N1)pdm09, and influenza A/Hong Kong/125/2017-like (H7N9), continue to emerge and infect humans; therefore, it is imperative that preparation be maintained for the next influenza pandemic. For this statistical analysis plan influenza A/Hong Kong/125/2017-like H7N9 will be referred to as H7N9.

The United States (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 Adjuvant System 03 (AS03), for administration with the vaccine antigens to improve the immunogenicity and achieve antigen dose-sparing.

Since the notification of emergence of a novel reassortant influenza A/H7N9 virus on 31 March 2013, 1568 laboratory-confirmed cases of human infection with avian influenza A/H7N9 virus in China have been reported to the World Health Organization (WHO), including 616 deaths. Most human infections, associated with poultry exposure, resulted in severe respiratory illness. Although some limited human-to-human infection has been reported, no sustained human-to-human H7N9 influenza virus transmission has been observed.

Vaccination is the primary measure to control the spread of influenza virus infection in humans. Efforts are therefore underway to develop vaccines that could mitigate the impact of an A/H7N9 influenza pandemic. GlaxoSmithKline Biologicals SA (GSK) has produced an investigational AS03-adjuvanted H7N9 virus vaccine and will conduct a clinical trial in the US to assess the safety and immunogenicity of different formulations of H7N9 split virus vaccine produced in GSK's Quebec facility, administered with AS03 adjuvant.

Influenza pandemics occur when a novel influenza virus emerges against which the vast majority of the world's population has no immunity. This phenomenon only occurs with Influenza A viruses and is attributed to the emergence of a new antigenic variant. This phenomenon, known as antigenic shift, typically represents introduction of a novel hemagglutinin (HA) antigen displayed on the surface of the virus, with or without a concomitant change in neuraminidase, the other major surface antigen. The reservoir of viruses bearing surface antigens to which humans are immunologically naïve is in wild water birds, and these viruses are believed to contribute their surface antigens to new strains capable of infecting humans by the process of gene reassortment, potentially occurring in swine or other domestic mammals. Alternatively, some strains of avian viruses may be able to invade human hosts directly; although these often replicate poorly and are transmitted inefficiently. If such a virus acquires the ability to spread efficiently from person to person, the potential result is a global outbreak of disease affecting

a high percentage of individuals in a short period of time, a pandemic; and this is likely to cause significant morbidity and mortality throughout the world.

GSK's clinical development program for immunization against influenza caused by potential pandemic subtypes deploys its proprietary AS03. This adjuvant system contains α-tocopherol (11.86 mg for "$AS03_A$"; 5.93 mg for "$AS03_B$") and squalene in an oil-in-water emulsion. Data with antigen-sparing formulations containing AS03 have been or are being generated in the context of multiple potential pandemic influenza threats.

Despite the development of antiviral drugs, vaccination remains the most effective way of controlling influenza during inter-pandemic periods. As part of US Department of Health and Human Services pandemic preparedness activities, the safety, immunogenicity, and dose-sparing ability of full and half doses of AS03 adjuvant in combination with H7N9 virus vaccine will be evaluated.

2 Objectives

2.1 Co-primary Objectives

Immunogenicity Objective

- To evaluate whether the monovalent A/Hong Kong/125/2017-like (H7N9) virus vaccine containing 1.9 µg, 3.75 µg, or 7.5 µg of HA adjuvanted with $AS03_A$ or $AS03_B$ elicits a hemagglutination inhibition (HI) antibody response to the vaccine-homologous virus that meets or exceeds the US Food and Drug Administration (FDA), Center for Biologics Evaluation and Research (CBER) immunogenicity criteria at the Day 43 visit.

Safety Objectives

- To describe the safety and reactogenicity of the different vaccine formulations through the Day 43 visit.
- To describe the safety of the different vaccine formulations through Month 13.

2.2 Secondary Objectives

- To describe the vaccine homologous H7N9 HI antibody profile in all study groups at Days 1, 22, and 43
- To describe the vaccine homologous H7N9 Microneutralization (MN) antibody profiles in a subset of participants at Days 1, 22, and 43

3 Investigational Plan

3.1 Overall Study Design and Plan

This is a Phase I/II, observer-blind, randomized, placebo-controlled, age stratified, multi-center study with 7 parallel groups, that will be conducted in the US.

The study will enroll approximately 840 participants randomly assigned to 1 of 7 groups of equal size to receive 2 doses of study vaccine or placebo administered intramuscularly 21 days apart. Each participant will participate for approximately 12 months after receipt of the final dose administered.

The enrollment will be performed to evenly distribute participants across the 2 age groups (18-64 years, ≥ 65 years) (i.e. of the 120 participants in each study group, 60 participants will be aged 18 to 64 years and 60 participants will be aged ≥ 65 years). Within the 18-64 years age group, the enrollment is further stratified into 18-49 years and 50-64 years to allow an even distribution of participants in terms of intervention allocation.

In addition, this study is also intended to capture coronavirus disease 2019 (COVID-19) cases among study participants based on the WHO criteria [27-Mar-2020 version]: suspected, probable, or confirmed. COVID-19 infection cases will be reported as AEs per normal reporting mechanisms. All AEs should be considered as to whether they meet serious adverse event (SAE) criteria, and if so, submitted through the SAE reporting mechanism. The COVID-19 eCRF page will be used to capture additional COVID-19 case details that would not normally be contained elsewhere in the eCRF.

Details of the study groups, interventions, and blinding foreseen in the study can be found in Table 1 and Table 2.

Table 1 Study Groups, Intervention and Blinding Foreseen in the Study

Intervention name	Vaccine/Product name	Study groups							Blinding
		190_B	190_A	375_B	375_A	750_B	750_A	Placebo	Observer-Blind
1.9 µg HA + AS03B	FLU-Q-PAN H7N9 (1.9)	●							●
	AS03B	●							●
1.9 µg HA + AS03A	FLU-Q-PAN H7N9 (1.9)		●						●
	AS03A		●						●

3.75 µg HA + AS03B	FLU-Q-PAN H7N9 (3.75)			●					●
	AS03B			●					●
3.75 µg HA + AS03A	FLU-Q-PAN H7N9 (3.75)				●				●
	AS03A				●				●
7.5 µg HA + AS03B	FLU-Q-PAN H7N9 (7.5)					●			●
	AS03B					●			●
7.5 µg HA + AS03A	FLU-Q-PAN H7N9 (7.5)						●		●
	AS03A						●		●
Placebo	Formulation buffer S9b							●	●

AS03A and AS03B refer to $AS03_A$ and $AS03_B$.
Formulation buffer S9b is a phosphate buffered saline.

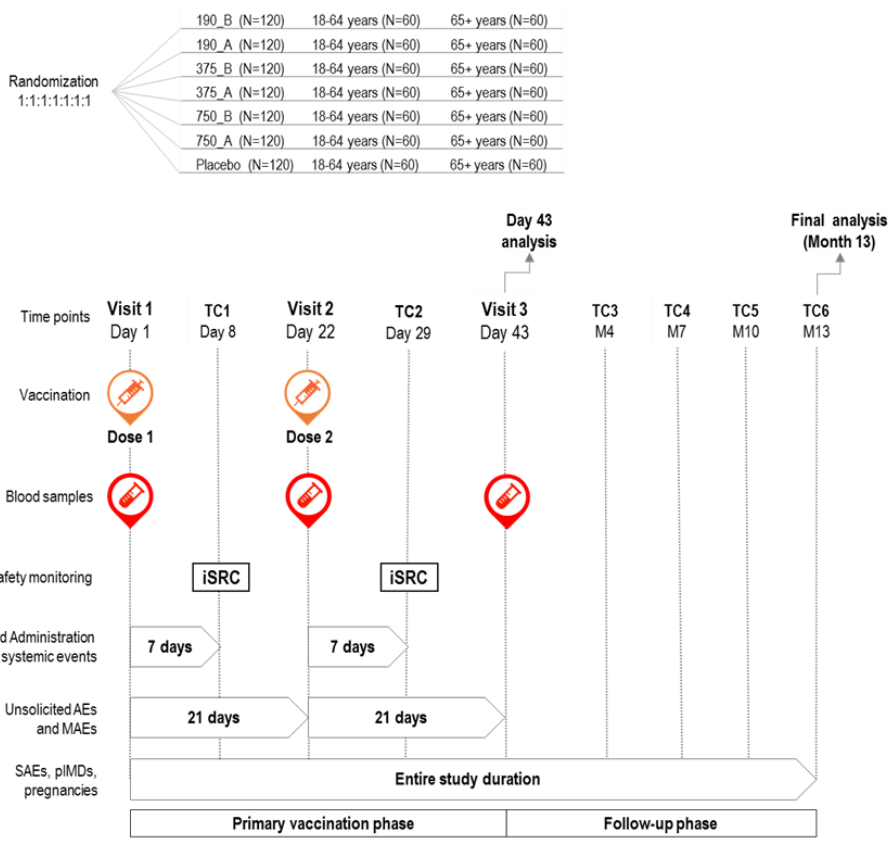
Table 2 Study Groups Foreseen in the Study

Study Intervention	Study Groups	Number of participants per study group	Age group	Number of participants per age group*
1.9 µg HA + AS03B	190_B	120	18 - 64 years	60
			≥ 65 years	60
1.9 µg HA + AS03A	190_A	120	18 - 64 years	60
			≥ 65 years	60
3.75 µg HA + AS03B	375_B	120	18 - 64 years	60
			≥ 65 years	60
3.75 µg HA + AS03A	375_A	120	18 - 64 years	60
			≥ 65 years	60
7.5 µg HA + AS03B	750_B	120	18 - 64 years	60
			≥ 65 years	60
7.5 µg HA + AS03A	750_A	120	18 - 64 years	60
			≥ 65 years	60
Placebo	Placebo	120	18 - 64 years	60
			≥ 65 years	60
Total number of participants		840		

AS03A and AS03B refer to $AS03_A$ and $AS03_B$.
* Within each of the 7 study groups, approximately 60 participants per age group will be enrolled with 57 evaluable participants accounting for possible 5% dropout.

The study design diagram is provided in Figure 1.

Figure 1 Study Design Overview



Note: Study groups and intervention (2 doses) to be administered: 190_B: 1.9 µg Hemagglutinin (HA) and $AS03_B$; 190_A: 1.9 µg HA and $AS03_A$; 375_B: 3.75 µg HA and $AS03_B$; 375_A: 3.75 µg HA and $AS03_A$; 750_B: 7.5 µg HA and $AS03_B$; 750_A: 7.5 µg HA and $AS03_A$; and Placebo: formulation buffer S9b (phosphate buffered saline).
Note: At least 2 internal Safety Review Committee (iSRC) reviews are planned. During each review, reactogenicity and safety data for approximately 140 participants (approximately 10 participants per vaccine group and placebo group) will be monitored. The first iSRC review will occur when data collected for 7 days post-Dose 1 (i.e. Day 1 to Day 7, inclusive) are available; the second review will occur based on the available data collected 7 days post-Dose 2 (i.e. Day 22 to Day 28, inclusive) for the same group of participants. Additional iSRC reviews may be carried out as needed (Protocol Section 8.2.2.2).
AE: adverse event; M: Month; MAE: medically attended adverse event; N: number of participants; pIMD: potential immune-mediated disease; SAE: serious adverse event; TC: telephone contact

Whenever possible, the investigator should arrange study visits within the optimal intervals described in Table 3. Visits that occur outside of the allowed intervals will be categorized as significant protocol deviations leading to the exclusion of a

participant from one of the Per Protocol sets (PPSx) or modified Per Protocol sets (mPPSx).

A detailed list of study procedures can be found in Section 13.

The informed consent of the participant must be signed before study participation. All inclusion and exclusion criteria will be checked as described in Protocol Sections 5.1 and 5.2 before dosing on Day 1.

On Visit 1 (Day 1) informed consent will be obtained and pre-vaccination procedures will be carried out. Upon satisfactory completion of pre-vaccination 1 procedures, participants will be randomized to a study group and intervention number and will have blood samples drawn before receiving the first dose of study vaccine.

Participants will be observed closely for at least 30 minutes following the administration of the vaccine, with appropriate medical treatment readily available in case of anaphylaxis and/or syncope.

Participants will have a second dose of study vaccine/product administered at Visit 2 following satisfactory completion of pre-vaccination 2 procedures. Participants will have blood drawn at Visit 1 pre-vaccination, Visit 2 pre-vaccination and Visit 3 to test for immune response.

An unsolicited AE is an AE that was not solicited using a Participant Diary and that was spontaneously communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs. Unsolicited AEs will be recorded for 21 days following administration of study vaccine/product. AEs will be recorded starting from informed consent date.

Serious adverse events (SAEs), medically attended AEs (MAEs), AEs/SAEs leading to withdrawal, SAEs related to study participation or concurrent GSK medication/vaccines and potential immune mediated diseases (pIMDs) will be recorded from the date of informed consent through Month 13. The pIMDs are listed in Protocol Table 19.

Solicited events include administration site and systemic events and are solicited using a Participant Diary. Solicited administration site events include pain, redness, and swelling. Solicited systemic events include fatigue, fever, gastrointestinal (nausea, vomiting, diarrhea, abdominal pain), headache, muscle ache, joint pain, shivering (chills), and sweating.

Participants will receive a safety follow-up call after each visit where study vaccine/product is administered. Solicited events will be recorded in participant diaries by the participant for 7 days after the vaccine/product is administered (including the day on which the vaccine/product is administered). For solicited events continuing after 7 days, the participant will be instructed to record events

until 21 days post-vaccination or until resolution. The participant will be instructed to return the completed diary card and COVID-19 assessment card to the investigator at the next study visit. Details on the timing and collection of the solicited administration site and systemic events on the diary card are described in the Study Procedures Manual.

Female participants who become pregnant after the first vaccination must not receive subsequent doses of the study vaccine/product, but may continue other study procedures at the discretion of the investigator.

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

Table 3 Intervals Between Study Visits

Interval (by visit number)	Interval (by visit name)	Optimal interval length[1] (Days)	Allowed interval (Study Day)
Visit 1 - TC1	Visit Day 1 - Telephone Contact Day 8	7	6-10
Visit 1 - Visit 2	Visit Day 1 - Visit Day 22	21	18-25[2]
Visit 2 - TC2	Visit Day 22 - Telephone Contact Day 29	7	26-30
Visit 2 - Visit 3	Visit Day 22 - Visit Day 43	21	38-46[2]
Visit 1 - TC3	Visit Day 1 - Month 4 Telephone Contact	90	80-100
Visit 1 - TC4	Visit Day 1 - Month 7 Telephone Contact	182	172-192
Visit 1 - TC5	Visit Day 1 - Month 10 Telephone Contact	270	260-280
Visit 1 - TC6	Visit Day 1 - Month 13 Telephone Contact	385	375-395

[1] The investigator should arrange study visits within this interval.
[2] Participants may not be eligible for inclusion in the Per Protocol analysis set (PPS) for immunogenicity analysis for the specified interval if blood collections are outside this interval. Refer to Section 4.6 for populations for analyses.
TC: telephone contact

At least 2 iSRC reviews are planned. During each iSRC review, reactogenicity and safety data for approximately 140 participants (approximately 10 participants per vaccine group and placebo group stratified by age) will be monitored. The first iSRC review will occur when data collected for 7 days post dose (i.e. Day 1 to Day 7, inclusive) are available; the second review will occur based on the available data collected 7 days post dose 2 (i.e. Day 22 to Day 28, inclusive) for the same group of participants. Additional iSRC reviews may be carried out as needed.

If a safety signal is observed, GSK may decide to suspend further vaccinations in all groups or in selected groups. Guidance about how to proceed will be provided should such a decision be made.

The safety holding rules are defined in Table 4. Holding rules 1a-b 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.

Table 4 Study Holding Rules

Holding Rule	Event	Number of Participants
1a	Death or any life-threatening SAE that can be reasonably attributed to the vaccination	≥ 1
1b	Any non-life-threatening SAE that can be reasonably attributed to the vaccination occurring within 21 days from vaccination	≥ 1

When a holding rule is identified the iSRC will review unblinded data.

3.2 Study Endpoints

3.2.1 Primary Endpoints

Immunogenicity Endpoints

- Humoral immune response in terms of vaccine-homologous HI antibody titers:
  - Seroprotection rate (SPR) at Day 43
  - Seroconversion rate (SCR) at Day 43

Safety Endpoints

- Occurrence of AEs
  - Solicited administration site events during a 7-day follow-up period (i.e. day of vaccination and 6 subsequent days) after each vaccination
  - Solicited systemic events during a 7-day follow-up (i.e. day of vaccination and 6 subsequent days) after each vaccination
  - Unsolicited AEs and MAEs for 21 days after each vaccination
  - SAEs, pIMDs up to Day 43 visit
  - pIMDs and SAEs until Month 13

3.2.2 Secondary Endpoints

Immunogenicity Endpoints

- Vaccine-homologous (H7N9) HI antibody titers for each study group:
  - Geometric Mean Titers (GMTs) at Days 1, 22, and 43
  - Seropositivity rates at Days 1, 22 and 43
  - SCR at Day 22
  - SPR at Days 1 and 22
  - Mean Geometric Increase (MGI) at Days 22 and 43
- Vaccine-homologous (H7N9) MN antibody titers for subset of participants:
  - GMTs at Days 1, 22, and 43
  - Seropositivity rates at Days 1, 22, and 43
  - Vaccine response rate (VRR) at Days 22 and 43

4 General Statistical Considerations

4.1 General Definitions

- Age will be calculated as the integer part of the difference between birth date and the treatment start date divided by 365.25. Birth date with missing day will be imputed as day 15 and birth data with missing day and month will be imputed as 30-June. For non-vaccinated subjects, age will be calculated considering Informed Consent date.

  The following Age groups will be created for the analysis:
  - "18 – 49 years" if calculated year is between the interval 18-49, including both values.
  - "50 – 64 years" if calculated year is between the interval 50-64, including both values.
  - "≥ 65 years" if calculated year is greater or equal to 65.
  - "65 – 74 years" if calculated year is between the interval 65-74, including both values.
  - "≥ 75 years" if calculated year is greater or equal to 75.
  - "18 – 64 years" if calculated year is between the interval 18-64, including both values (only for web disclosure table).

  - "65 – 84 years" if calculated year is between the interval 65-84, including both values (only for web disclosure table).
  - "≥ 85 years" if calculated year is greater or equal to 85 (only for web disclosure table).

- The antibody titer cut-off value for HI will be set as 10 1/dilution [DIL].
- The LLOQ (cut-off) of Q^2 MN assay with the A/Hong Kong/125/2017-like (H7N9) will be set as 28.3 NT_{50}. In case a different RBC will be used the new cut-off value will be confirmed with the lab. A footnote will be added in all MN-related tables confirming the cut-off value used in the analyses.
- A seronegative participant is a participant whose antibody titer is below the cut-off value.
- A seropositive participant is a participant whose antibody titer is greater than or equal to the cut-off value.
- Seroconversion for HI is defined as a post-vaccination antibody titer ≥ 40 1/DIL in the serum of participants seronegative before vaccination (i.e. titer < assay cut-off at Day 1). For seropositive participants (i.e. titer ≥ assay cut-off at Day 1), seroconversion will require a 4-fold rise in post-vaccination HI antibody titer (but at least a titer of 40 1/DIL).
- SCR is defined as the percentage of participants who seroconvert post-vaccination.
- Seroprotection rate for HI is defined as the percentage of participants with an HI antibody titer ≥ 40 1/DIL.
- MGI is defined as the geometric mean of the within-subject ratios of the post-vaccination HI antibody titer to the Day 1 HI antibody titer.
- Vaccine response for MN is defined as at least a 4-fold increase in antibody titer as compared to the antibody titer at Day 1 (pre-vaccination). Antibody titers below the cut-off of the assay are given an arbitrary value of half the cut-off for the purpose of vaccine response calculation.
- Vaccine Response Rate (VRR) for MN is defined as the percentage of participants with vaccine response.

4.2 Data Transformations and Display

Interventions will be labelled on all outputs as described in Table 5.

Table 5 Intervention Labels

Intervention Number	Intervention Label
1	1.9 ug HA + AS03B
2	1.9 ug HA + AS03A
3	3.75 ug HA + AS03B
4	3.75 ug HA + AS03A
5	7.5 ug HA + AS03B
6	7.5 ug HA + AS03A
7	Placebo

AS03A and AS03B refer to $AS03_A$ and $AS03_B$.

Strata will be labelled on all outputs as described in Table 6.

Table 6 Strata Labels

Strata Number	Strata Label
1	18 - 49 years
2	50 – 64 years
3	≥ 65 years

Summaries will be presented by each study group, age group, and overall. The ≥ 65 years age group will also be presented by 65-74 years, ≥ 75 years, and overall.

Data will be displayed in all listings sorted by study group and age group. Participants will be identified in the listings by the participant identification number.

Categorical data will be described using the participant count and percentage in each category. For a given participant and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. A row denoted 'Missing' will be displayed to account for missing values in categorical summaries. The 'Missing' row will only be displayed if at least one study group has a non-zero count for this category. Note percentages will not be displayed in the 'Missing' row, to draw attention to the percentages for the non-missing categories. Unless specified otherwise, percentages for analysis of unsolicited

AEs will be based on the number of participants vaccinated in each study group and age group within the analysis population, and percentages for the analysis of immunogenicity data and solicited events will be based on the number of participants with non-missing data in each study group and age group within the analysis population. Percentages will not be displayed if the corresponding count is zero, in order to draw attention to the percentages for non-zero counts. Percentages will be displayed using one decimal place.

Continuous data will be described using descriptive statistics (i.e. n, mean, standard deviation, minimum and maximum). For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean will be displayed to one level of precision greater than the data collected. Standard deviation/standard error will be displayed to two levels of precision greater than the data collected.

If statistical analysis cannot be performed for a particular age group or study group, then these should be displayed as “NC.” (not calculated). Confidence intervals that cannot be calculated should be displayed as “(NC.)”.

For the primary immunogenicity analysis, which will be reported at Day 43 the overall type I error rate is fixed at 5% (two-sided tests) and a Bonferroni adjustment will be applied to allow simultaneous multiple comparisons of each antigen/adjuvant group. No further adjustment will be used since the tests will be applied sequentially. For the secondary immunogenicity and primary safety analyses no adjustment for multiple comparisons will be made in each antigen/adjuvant group as the analyses are descriptive. Confidence intervals (CIs) will be presented and p-values will not be presented. For the secondary immunogenicity and safety analyses, CIs are presented for descriptive purposes only.

Baseline will be defined as the value recorded at Visit 1. The study day will be calculated as assessment date - first dose date of study vaccine + 1 if the study date is on or after first dose date of study vaccine, or assessment date – first dose date of study vaccine if the study date is prior to the first dose date of study vaccine.

Throughout the study, logarithmic transformations and anti-logarithms will use base 10.

Statistical analysis will be performed using SAS® Version 9.4 or higher. Standardized and validated SAS macros from PPD will be used to set up table, listing, figure formats (headers/footers and tabulation format) and tabulate the summaries. All tables and listings will be independently validated using double programming; datasets behind the figures will be independently validated using double programming and figure outputs will be independently validated manually.

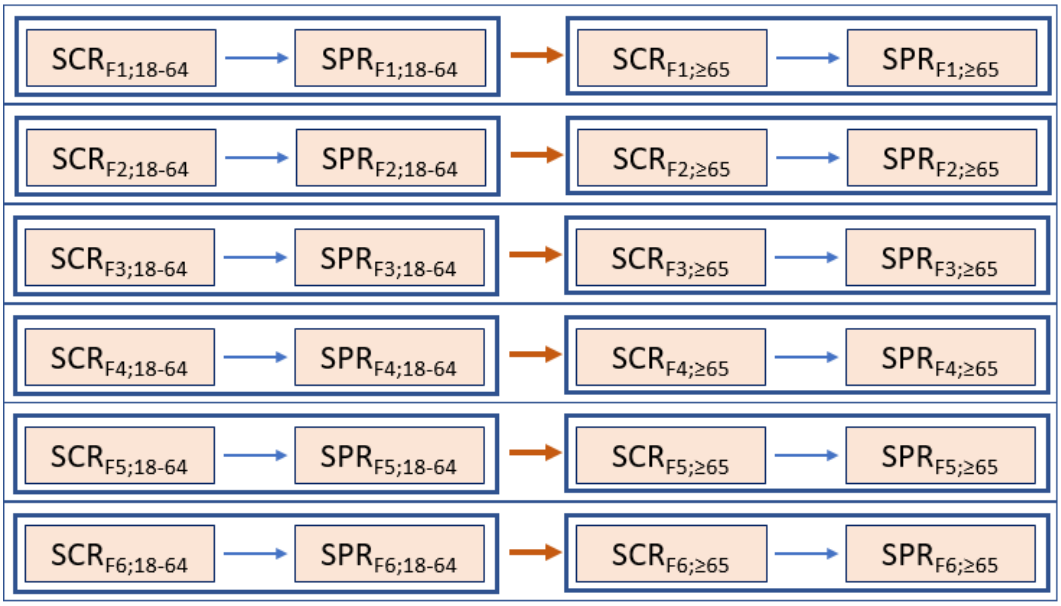
4.3 Sample Size

The primary immunogenicity objective of the study is to evaluate whether vaccination with monovalent H7N9 virus vaccine containing 1.9 µg, 3.75 µg or 7.5 µg of HA adjuvanted with $AS03_A$ or $AS03_B$ elicits an HI antibody response to the vaccine-homologous virus that meets or exceeds the US FDA, CBER immunogenicity criteria at the Day 43 visit.

The age-appropriate CBER criteria will be used and assessed separately:

- CBER immunogenicity criteria for SCR for 18 to 64 years of age will be shown if the lower limit (LL) of the 99.17% CI for SCR meets or exceeds 40%.
- CBER immunogenicity criteria for SPR for 18 to 64 years of age will be shown if the LL of the 99.17% CI for the incidence rate of HI Reciprocal Titers ≥ 40 meets or exceeds 70%.
- CBER immunogenicity criteria for SCR for ≥ 65 years of age will be shown if the LL of the 99.17% CI for seroconversion rate meets or exceeds 30%.
- CBER immunogenicity criteria for SPR for ≥ 65 years of age will be shown if the LL of the 99.17% CI for the incidence rate of HI Reciprocal Titers ≥ 40 meets or exceeds 60%.

The statistical testing sequence is illustrated below. The 6 antigen/adjuvant combinations will be assessed simultaneously for a particular endpoint (SCR or SPR) and age category using Bonferroni Type 1 error adjustment. The order of statistical testing is SCR for 18-64 years of age, SPR for 18-64 years of age, SCR for ≥65 years of age, SPR for ≥65 years of age. Testing will progress in the sequence only if current test is a success, so that no further adjustment of alpha is needed. Success is reached if at least one antigen/adjuvant combination does fulfill the CBER requirements for SCR and for SPR for at least one age category after all permitted statistical tests are completed.



F1: 1.9 µg HA + AS03B; F2: 1.9 µg HA + AS03A; F3: 3.75 µg HA + AS03B; F4: 3.75 µg HA + AS03A; F5: 7.5 µg HA + AS03B; F6: 7.5 µg HA + AS03A

A total of 840 participants are planned to be enrolled, with 60 participants per antigen/adjuvant/age group. A drop-out/protocol violation rate of not more than 5% yields an approximate sample size of 57 evaluable participants per group, giving 82% overall power to fulfil the CBER (SCR, SPR) immunogenicity criteria in any one of the 12 adjuvanted vaccine intervention groups, assuming that the reference rate for SPR and SCR is 91% and 80% for participants 18 to 64 years of age and 86% and 75% for participants ≥ 65 years of age, respectively.

The 2-sided exact Clopper-Pearson 99.17% CI for SCR or SPR is to allow parallel assessment of the 6 antigen/adjuvant combinations addressing multiple comparisons using a Bonferroni adjustment by dividing the 5% Type I error (two-sided tests) equally 6 ways. Success can be declared for any antigen/adjuvant group if CBER criteria is met even if any other group does not meet the CBER criteria.

Table 7 presents the power for 1 group to meet the CBER immunogenicity criteria, assuming the enrollment is 60 participants per group and non-evaluable rate is about 5%.

Table 7 Criteria to Evaluate Primary Objective with Respect to SCR and SPR for Anti-HA, 21 Days After the Second Vaccination

To meet CBER Criteria	Endpoint	Stage in testing sequence	Statistical Success Criteria	N evaluable	Reference value	Power*
18-64 years of age	Anti-HA: SCR	1	LL of 99.17% two-sided CI of SCR > 40%	57	80%	99.99%*
	Anti-HA: SPR	2	LL of 99.17% two-sided CI of SPR > 70%	57	91%	86.26%*
≥65 years of age	Anti-HA: SCR	3	LL of 99.17% two-sided CI of SCR > 30%	57	75%	>99.99%*
	Anti-HA: SPR	4	LL of 99.17% two-sided CI of SPR > 60%	57	86%	95.12%*
				Overall power		82%

* Power estimated using PASS 2012, 1-Sided Exact test on the proportions, alpha = 0.415%. Overall power is the product of power for the 4 hypotheses within a formulation across the 2 age groups.
CBER: Center for Biologics Evaluation and Research; CI: confidence interval; HA: hemagglutinin; LL: lower limit; SCR: seroconversion rate; SPR: seroprotection rate.

4.4 Randomization, Stratification, and Blinding

The enrollment will be performed to evenly distribute participants across the 2 age groups (18-64 years, ≥ 65 years) (i.e. of the 120 participants in each study group, 60 participants will be aged 18 to 64 years and 60 participants will be aged ≥ 65 years). Within the 18-64 years age group, the enrollment is further stratified into 18-49 years and 50-64 years to allow an even distribution of participants in terms of intervention allocation.

Allocation of the participant to a study group at the investigator site will be performed using central randomization on the PPD Interactive Response Technology (IRT).

The study will enroll approximately 840 participants randomly assigned to 1 of 7 groups of equal size to receive 2 doses of study vaccine or placebo administered intramuscularly 21 days apart. Each participant will participate for approximately 12 months after receipt of the final dose administered.

This is an observer-blinded study. Data will be collected in an observer-blind manner. To do so, vaccine/product will be prepared and administered by qualified study personnel who will not participate in data collection, evaluation, review or the entry of any study endpoint (i.e. reactogenicity, safety, immunogenicity).

The laboratory in charge of the sample testing will be blinded to the intervention assignment. Codes will be used to link the participant and study (without any link to the intervention attributed to the participant) to each sample.

Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. In order to maintain this blind, an otherwise uninvolved third party will be responsible for the reconstitution and dispensation of all study intervention and will endeavor to ensure that there are no differences in time taken to dispense following randomization.

This third party will instruct the participant to avoid discussing the dosing site or visual appearance of the study intervention with the investigator. Unblinded monitors, and in the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that the randomization/dispensing has been done accurately.

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted.

A statistical team will be unblinded for the interim analysis outlined in Section 10.2 and will prepare the iSRC analyses outlined in Section 10.1.

4.5 Data Handling

Analysis Visit Names for Immunogenicity Analysis

Study visits will be derived as in Table 8. Analysis Visit names (AVISIT) will be used within the Immunogenicity and Safety Analyses.

Table 8 Analysis Visit Names

Visit Name	AVISIT
Visit 1 Day 1	V1 DAY 1
Telephone Contact 1 Day 8	SC1 DAY 8
Visit 2 Day 22	V2 DAY 22
Telephone Contact 2 Day 29	SC2 DAY 29
Visit 3 Day 43	V3 DAY 43
Telephone Contact 3 Month 4	SC3 MONTH 4
Telephone Contact 4 Month 7	SC4 MONTH 7
Telephone Contact 5 Month 10	SC5 MONTH 10
Telephone Contact 6 Month 13	SC6 MONTH 13

Note: Vx = Visit x, SCx=Safety Call x.

Titer Results

For a given participant and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Summaries and analyses will be performed using all available non-missing titer results for the included population.

Titer results recorded as below the cut-off will be imputed with a numeric value of half the cut-off for summaries and analyses and will be listed as reported in the raw data. For example, if an assay records a cut-off of 10 for HI and a sample is reported to have "< 10" as the titer level, a value of 5 will be used for the statistical summaries and analyses. Titer results recorded as "1:x" (where x is the dilution factor) will be assigned a numeric value of x. Titer results recorded as ">1:x" will be assigned a numeric value of x to be used for the statistical summaries and analyses.

The cut-off values for antibody titer are defined by the laboratory before the analysis, and will be specified in the CSR.

Missing Data

For safety analyses, participants who missed reporting symptoms (solicited or unsolicited), concomitant medications, or concomitant vaccinations will not be imputed but will be presented as missing for the summaries.

In order to minimize the effect of missing data, the study period will be divided into time intervals for the safety analyses. For unsolicited AEs, the study period will be divided into the following intervals: all unsolicited AEs and MAEs reported from Day 1 to Day 21 after each vaccination, AEs leading to premature withdrawal from the study during the entire study period, SAEs reported during the entire study period and pIMD reported during the study period for the Exposed Set. Unsolicited AEs will be assigned to the study periods based upon the start date and times recorded in the eCRF. Concomitant medications will be assessed up to 21 days after each vaccination for the Exposed Set in a summary table. All concomitant medications collected in the database will presented in a data listing.

A participant will be classified as having missing data within the specified intervals as described below:

Category	**Regarded as Missing When:**
Non serious AEs	No AEs are recorded and there is no response to "Have any non-serious adverse events occurred which are required to be reported as per protocol?" (Non Serious Adverse Event YN electronic Case Report Form [eCRF] page).
Medically attended AEs	If AEs are recorded and there is no response to "Medically attended visit" (Non Serious Adverse Events eCRF page or Serious/Expedited Event eCRF page).
AEs leading to withdrawal from the study vaccine	If AEs are recorded and there is no response to "Action Taken with study vaccine(s) as a Result of the AE" (Non Serious Adverse Events eCRF page or Serious/Expedited Event eCRF page).

Serious AEs	If no SAEs are recorded and there is no response to "Did the subject experience any Serious Adverse Event and/or pIMD and/or other AESI and/or Non-Serious related AE (ADR) that are required to be reported per protocol?" (Serious/Expedited Event YN eCRF page), or if the answer was "Yes" and there is no response to "Serious?" (Serious/Expedited Event eCRF page).
pIMD	No pIMD events recorded and there is no response to "Did the subject experience any Serious Adverse Event and/or pIMD and/or other AESI and/or Non-Serious related AE (ADR) that are required to be reported per protocol?" (Serious/Expedited Event YN eCRF page), or if the answer was "Yes" and there is no response to "Adverse Event of Special Interest (AESI)?" (Serious/Expedited Event eCRF page).
Concomitant medications	If no concomitant medications are recorded on the Concomitant Medications eCRF page, and there is no response to "Have any medications that are required to be reported per protocol been taken?" on the Concomitant Medications and Vaccinations YN eCRF page.
Concomitant vaccinations	If no concomitant vaccinations are recorded on the Concomitant Medications and Vaccinations eCRF page, and there is no response to "Have any vaccines required to be reported as per protocol other than study vaccine(s) been administered?" on the Concomitant Medications and Vaccinations YN eCRF page.

Missing Values for Solicited Adverse Events When Leading Questions Have Been Answered

The eCRF pages Solicited Administration Site Events and Solicited Systemic Events contain the following leading questions:

- Did the subject experience any of the solicited systemic signs/symptoms between Day 1 and Day 7?
- Did the subject experience any solicited administration site events between Day 1 and Day 7?

If the answer is 'No' then the investigator is asked not to complete the intensities or measurements for the individual symptoms and individual timepoints. Values in the solicited adverse events dataset will be set as 'None' (for intensity) or '0' (for measurement).

The analysis of solicited systemic symptoms will include all subjects for whom the question about the presence of a solicited systemic symptoms has been answered by 'Yes' or 'No'. If the answer is 'No', the subject will be considered as not having that symptom after that dose. If the answer is "Yes", the maximum intensity recording over the considered follow-up period will be used for the analysis of the percentage of subjects with symptoms.

Subjects who documented the presence of a specific symptom (e.g. fever, fatigue, etc.) but partially recorded daily measurement (e.g. intensity missing for Day 3) over the considered solicited period will be included in the summaries and classified according to their maximum observed daily recording over the solicited period.

When no daily measurement is recorded when the presence of a symptom is Yes,

- For the symptoms Headache, Fatigue, Muscle aches, Gastrointestinal Symptoms (nausea, vomiting, diarrhea and/or abdominal pain), Joint Pain, Shivering (chills), and Sweating; those subjects will not be counted in the summary of subjects with a symptoms by grade but will be part of the summary corresponding to the 'All' category

- For Fever, those subjects will not be counted in the summary of subjects with symptoms above a specified threshold, however they will be part of the summary corresponding to the 'All' category.

The analysis of solicited local symptoms will include all subjects for whom the question about the presence of a solicited local symptoms has been answered by 'Yes' or 'No'.

For each solicited administration site symptom, if the answer to the presence of a local symptom is 'No', the subject will be considered not having that administration site symptom at the injection site after that dose. If the answer to is 'Yes', the maximum intensity recording over the considered follow-up period will be used for the analysis of the percentage of subjects with symptoms.
Subjects who documented the presence of a symptom but partially recorded daily measurement over the solicited period will be included in the summaries and classified according to their maximum observed daily recording over the solicited period.

Subjects who have documented the presence of a symptom without any recorded daily measurement from Day 1 to Day 7 will not be counted in the summary of subjects with each grade, however they will be part of the summary corresponding to the 'Any' category.

4.6 Analysis Sets

4.6.1 Enrolled Set

All participants who agreed to participate in a clinical study after completion of the informed consent process.

4.6.2 Randomized Set

All participants who were randomized to receive a study vaccine

4.6.3 Exposed Set

All participants who received any study vaccination. The allocation in a group is done in function of the administered intervention. The analysis of primary and secondary safety endpoints will be based on this set.

4.6.4 Full Analysis Sets (FASx)

Full Analysis Set 1

- All participants in the Exposed Set who have post-vaccination immunogenicity data at Visit 3 (Day 43). Participants will be analyzed as "randomized" (i.e. according to the vaccine[s] the participant was randomized to receive).

Full Analysis Set 2

- All participants in the Exposed Set who have post-vaccination immunogenicity data at Visit 2 (Day 22). Participants will be analyzed as "randomized" (i.e. according to the vaccine[s] the participant was randomized to receive).

4.6.5 Per Protocol Set (PPSx)

Per Protocol Set 1

- The PPS 1 is a subset of FAS 1. The PPS 1 includes all FAS 1 participants with no major protocol deviations that lead to exclusion at or prior to Visit 3 (Day 43). Primary immunogenicity data will be evaluated based on this set.

Per Protocol Set 2

- The PPS 2 is a subset of FAS 2. The PPS 2 includes all FAS 2 participants with no major protocol deviations that lead to exclusion at or prior to Visit 2 (Day 22). Secondary immunogenicity data will be evaluated based on this set.

Major protocol deviations leading to exclusion are described in Section 5.2 and the Study Deviation Rules document and will be finalized prior to the interim analysis defined in Section 10.2.

4.6.6 Modified Per Protocol Set (mPPSx)

Modified Per Protocol Set 1 (mPPS1)

- *The mPPS 1 is a subset of FAS 1. The mPPS 1 includes all FAS 1 participants with no major protocol deviations (check major protocol deviations definition in Section 5.2) that lead to exclusion at or prior to Visit 3 (Day 43). The time window between Visit 1 and Visit 2 that is permitted for inclusion in this analysis set is 18-32 days. The time window between Visit 2 and Visit 3 that is permitted for inclusion in this analysis set is 14-32 calendar days.*

All major protocol deviations which lead exclusion from PPS1 will also lead exclusion from mPPS1. Only the major protocol deviations related to sample collection date or vaccination date outside to the intervals described above will not lead exclusion from mPPS1.

Modified Per Protocol Set 2 (mPPS2)

- *The mPPS 2 is a subset of FAS 2. The mPPS 2 includes all FAS 2 participants with no major protocol deviations that lead to exclusion at or prior to Visit 2 (Day 22). The time window between Visit 1 and Visit 2 that is permitted for inclusion in this analysis set is 18-32 days.*

Major protocol deviations leading to exclusion are described in Section 5.2 *and the Study Deviation Rules document and will be finalized prior to the interim analysis defined in Section* 10.2.

4.6.7 Microneutralization Set

All participants in the Randomized Set who were also selected to the subset of MN evaluation.

4.6.8 Microneutralization Per Protocol Set (MNPPSx)

Microneutralization Per Protocol Set 1

- All participants in the MN Set who are also part of the PPS 1.

Microneutralization Per Protocol Set 2

- All participants in the MN Set who are also part of the PPS 2.

4.6.9 Microneutralization modified Per Protocol Set (MNmPPSx)

Microneutralization modified Per Protocol Set 1

- All participants in the MN Set who are also part of the mPPS 1.

Microneutralization Per Protocol Set 2

- All participants in the MN Set who are also part of the mPPS 2.

5 Participant Disposition

5.1 Disposition

Participant disposition will be summarized as treated for the Exposed Set, and for each study group, age group, and overall. The summary of participant disposition as enrolled will include the number and percentage of participants who were randomized, screen failures, and major reason for screen failure. The summary of participant disposition as treated will include the number of participants in each analysis set defined in Section 4.6, the number and percentage of participants who received any and each study vaccination, the number and percentage of participants who completed the study and the primary reason for withdrawal from the study, the number and percentage of participants who completed the study vaccinations and the primary reason for withdrawal of study vaccination.

Listings will be provided for disposition data based on the Enrolled Set.

5.2 Major Protocol Deviations

A major protocol deviation leading to exclusion is defined as a protocol deviation that is considered to have a significant impact on the immunogenicity results of the participant and will cause a participant to be excluded from the per-protocol analysis sets (PPSx, mPPSx, MN PPSx and MN mPPSx). The number and percentage of participants with each significant protocol deviation leading to exclusion from per-protocol analysis sets will be presented for the Exposed Set, and a listing will also be provided. Major protocol deviations leading to exclusions from PPSx, mPPSx, MN PPSx and MN mPPSx will be summarized by study group, age group, and overall for the Exposed Set.

All protocol deviations will be identified prior to the analysis and a clinical judgment will be necessary to classify each deviation as “major” or “minor”. Key major deviations are provided below, but not limited to:

- Participants enrolled who did not sign the informed consent
- Participants enrolled who signed the wrong informed consent version
- Participants enrolled who included fraudulent data

- Participants enrolled who did not meet entry criteria including age at enrollment
- Participants who received incorrect treatment number
- Participants who were unblinded before end of the study
- Participants incorrectly vaccinated
- Participants who did not receive study vaccinations as planned in protocol
- Participants who did not do the corresponding vaccination visit
- Participants who did not have 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
- Participants who reported taking any prohibited vaccination/therapy as listed in protocol

These key major deviations will be assessed based on the data collected in the eCRFs. The complete list of protocol deviations considered major for this study will be reported in the CSR. If a participant incurs a condition that has the capability of altering their immune response, this will be recorded as an AE and identified as a significant protocol deviation by medical monitoring.

The terms ‘major’ and ‘significant’ for protocol deviations are used interchangeably in study documents and have the same meaning.

Significant protocol deviations leading to exclusion in each of the study populations is described in Table 9.

Table 9 Significant Protocol Deviation that leads in an exclusion

Protocol Deviation	Enr	Rand	Exp	FAS1	FAS2	PPS1	PPS2	mPPS1	mPPS2	MNPPS1	MNPPS2	MNmPPS1	MNmPPS2
Invalid informed consent or fraud in data	X	X	X	X	X	X	X	X	X	X	X	X	X
Incorrect treatment number provided at V2						X		X		X		X	
Unblinding of subject by sponsor/CRO personnel not done per study procedures at V1						X	X	X	X	X	X	X	X
Unblinding of subject by sponsor/CRO personnel not done per study procedures at V2						X		X		X		X	
Investigational vaccine administrated at V1 Day 1 even though subject met exclusion						X	X	X	X	X	X	X	X
Persistent inadequate source documents management after re-education**							X		X		X		X
Vaccine temperature deviation at V1						X	X	X	X	X	X	X	X
Vaccine temperature deviation at V2						X		X		X		X	
Inclusion/Exclusion criteria not meet						X	X	X	X	X	X	X	X
Study vaccine dose not administered according to protocol for V1: Wrong site/route injection/, wrong reconstitution, incorrect volume, Expired vaccine administered						X	X	X	X	X	X	X	X
Study vaccine dose not administered according to protocol for V2: Wrong site/route injection, wrong reconstitution, incorrect volume, Expired vaccine administered						X		X		X		X	

Protocol Deviation	Enr	Rand	Exp	FAS1	FAS2	PPS1	PPS2	mPPS1	mPPS2	MNPPS1	MNPPS2	MNmPPS1	MNmPPS2
Subsequent vaccine administered while contraindicated at V1						X	X	X	X	X	X	X	X
Subsequent vaccine administered while contraindicated at V2						X		X		X		X	
Incomplete treatment course V1						X	X	X	X	X	X	X	X
Incomplete treatment course V2						X		X		X		X	
Vaccination date at V2 done outside of the interval between V1 and V2 of 18-25 Days						X				X			
Vaccination date at V2 done outside of the interval between V1 and V2 of 18-32 Days								X				X	
Serological results collected but not available at V1						X	X	X	X	X	X	X	X
Blood sample at V1: not taken, not available, low serum volume, Lab error (spinning …), temperature deviation						X	X	X	X	X	X	X	X
Blood sample at V2: not taken, not available, low serum volume, Lab error (spinning …), temperature deviation					X*		X		X		X		X
Blood sample at V3: not taken, not available, low serum volume, Lab error (spinning …), temperature deviation				X*		X		X		X		X	
Blood sample collection at V2 done outside of the interval between V1 and V2 of 18-25 Days							X				X		

Protocol Deviation	Enr	Rand	Exp	FAS1	FAS2	PPS1	PPS2	mPPS1	mPPS2	MNPPS1	MNPPS2	MNmPPS1	MNmPPS2
Blood sample collection at V2 done outside of the interval between V1 and V2 of 18-32 Days									X				X
Blood sample collection done at V3 outside of the interval between V2 and V3 of 14 - 32 calendar Days								X				X	
Blood sample collection at V3 done outside of the interval between 38 - 46 Study Days						X				X			
Subjects MN1 and MN2, who were randomized to MN set but were not included										X	X	X	X
Temperature deviations from range defined in protocol and/or SPM for vaccine stored in fridge (0-8C; site level) at V1						X	X	X	X	X	X	X	X

* Subject elimination from FAS 1 or FAS 2 must only take place in cases where blood sample results are not available for any reason above described
** Elimination will be based on case-by-case bases
Enr = Enrolled set; Exp = Exposed set; Rand = Randomized set; FAS = Full Analysis Set; PPS = Per Protocol Set; mPPS = modified Per Protocol Set; MNPPS = Microneutralization per protocol set; MNmPPS = Microneutralization modified per protocol set.
X = Exclusion from the study population set

6 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized for the Exposed Set, Enrolled Set, PPS1, PPS 2, mPPS1, mPPS2, presented by study group, age group, and overall. Participant demographic and baseline characteristics will also be presented in a listing for the Enrolled Set.

6.1 Demographics

The demographic characteristics consist of gender, race, ethnicity, and center. The number and percentage of participants by gender (Male, Female), race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, and Other), ethnicity (Hispanic or Latino, Not Hispanic or Latino) and center, will be reported.

Demographics will be summarized using frequency counts and percentages.

6.2 Baseline Characteristics

The baseline characteristics consist of age (years), age group, baseline height (cm), baseline weight (kg), and baseline body mass index (BMI) (kg/m^2). Age group will be based on the age recorded on the eCRF. BMI is calculated as (body weight in kilograms) / (height in meters)^2 and will be calculated to 2 decimal places.

Age (years, as recorded on the eCRF), baseline height (cm), baseline weight (kg), and baseline BMI (kg/m^2) will be summarized using descriptive statistics.

Additionally, for web disclosure requirement, the number and percentage of subjects in the following age categories will be presented for the Enrolled Set: 18-64 years, 65-84 years, ≥85 years.

6.3 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version to be delineated in the CSR. The number and percentage of participants with any medical history will be summarized overall and for each system organ class and preferred term by study group. Percentages will be calculated based on number of participants in the Exposed Set by study group, age group, and overall.

Participant medical history data will also be presented in a listing for the Exposed Set.

6.4 Inclusion and Exclusion Criteria

Participants who did not meet inclusion criteria or met exclusion criteria will be presented in a listing for the Enrolled Set. Inclusion and exclusion criteria are listed in the protocol sections 5.1 and 5.2.

7 Treatments and Medications

7.1 Vaccination History, Concomitant Vaccinations, and Concomitant Medications

All vaccinations and medications will be coded according to the GSK Drug dictionary (GSKDrug), version to be delineated in the CSR. Concomitant medications are also collected for any SAE and pIMD per protocol section 6.5.

7.1.1 Vaccination History and Concomitant Vaccinations

The number and percentage of participants with any prior and concomitant vaccinations recorded on the eCRF will be summarized by study group, age group, and overall. A concomitant vaccination is defined as a vaccination administered in the period starting from the first dose of study vaccine(s) and ending at the last study visit (Day 43). Prior and concomitant vaccinations will be displayed in a listing. All summaries and listings will be performed using the Exposed Set.

7.1.2 Concomitant Medications

Concomitant medications are defined as any medications/products, except vitamins and dietary supplements, associated with an AE administered through EOS.

The number and percentage of participants with at least one concomitant medication will be summarized by study group, age group, and overall and the number and percentage of participants taking each medication will be presented by preferred term. Concomitant medications will be displayed in a listing. All summaries and listings will be performed using the Exposed Set. Participants with missing concomitant medication data will be handled as described in Section 4.5.

7.2 Extent of Exposure

Extent of exposure will be based on the Exposed Set and will be presented by study group, age group, and overall.

7.2.1 Compliance

The number and percentage of participants who received any study vaccination will be presented, as well as the number and percentage of participants who received all expected vaccinations during the study and the number and percentage of participants who withdrew from study vaccine. A participant has withdrawn from study vaccine if vaccination was administered at Visit 1, no vaccination was administered at Visit 2 and the participant has data recorded for at least one of the following: Telephone Contact Day 8 or Visit 2.

In addition, the number and percentage of participants who did not receive all vaccinations with reason (including participants who received a partial vaccination) will be displayed by visit. All study groups and age group are expected to receive 2 vaccinations; one at Visit 1 and one at Visit 2.

7.2.2 Visit Attendance

The number and percentage of participants who attended a visit or received a safety call within the interval described in Table 3 and per the naming conventions in Table 8 will be presented for the following visits:

- Visit 1 Day 1
- Telephone Contact 1 Day 8
- Visit 2 Day 22
- Telephone Contact 2 Day 29
- Visit 3 Day 43
- Telephone Contact 3 Month 4
- Telephone Contact 4 Month 7
- Telephone Contact 5 Month 10
- Telephone Contact 6 Month 13

The number and percentage of participants with attendance at each study visit will be summarized by study group, age group, and overall for the Exposed Set. Listings will be provided for the Exposed Set to provide details of visit attendance, safety calls, and blood samples.

An additional table with the number and percentage of participants with a deviation from the study and with the minimum and maximum days deviated will be generated by treatment group and overall.

The deviation intervals included in this table for the PPSx and MNPPSx will be:

- Between 18 – 25 days from Visit 1 to Visit 2
- Between 38 – 46 days from Visit 2 to Visit 3

The deviation intervals included in this table for the mPPSx and mMNPPSx will be:

- Between 18 – 32 days from Visit 1 to Visit 2
- Between 14 – 32 days from Visit 2 to Visit 3

A table with all deviations from intervals according to Table 3 will be added in the final analysis.

8 Immunogenicity Analysis

The primary immunogenicity objective of this study is to evaluate whether the vaccine with monovalent H7N9 virus containing 1.9 µg, 3.75 µg, or 7.5 µg of HA adjuvanted with $AS03_A$ or $AS03_B$ elicits a HI antibody response to the vaccine-homologous virus that meets or exceeds the US FDA, CBER immunogenicity criteria at the Day 43 visit. Section 4.3 defines the conditions under which the observed immune responses will meet the guidelines.

The secondary immunogenicity objectives of this study are to describe the vaccine homologous H7N9 HI and MN antibody profiles at Days 1, 22, and 43.

The primary and secondary H7N9 HI immunogenicity analyses will be based on the applicable PPSx as described in section 4.6. Supplementary analyses for primary and secondary HI immunogenicity analyses will be based on the applicable mPPSx. Results for baseline values will be presented using PPS2 and mPPS2 accordingly. If the difference between PPS 1 and FAS 1 is greater than 10%, a second analysis based on the applicable FASx will be performed to complement the PPSx analysis.

The H7N9 MN immunogenicity analyses will be based on the applicable MNPPSx as described in section 4.6. Supplementary analyses for MN immunogenicity analyses will be based on the applicable MN mPPSx.

For a given participant and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced.

Titers below cut-off will be handled as described in Section 4.5.

H7N9 HI titer results will be listed for the Exposed Set and the listing will indicate participants included in each of PPSx, mPPSx and FASx. The listing will also indicate participants with HI titers ≥ cut-off and participants who experienced a 4-fold increase in HI titers since baseline. A similar listing will also be prepared for the H7N9 MN titer results for the MN Set and the listing will indicate participants included in each of MNPPSx and MNmPPSx.

For the remainder of Section 8 the Analysis Visit names defined in Table 8 will be used.

The primary and secondary immunogenicity analyses will be presented in the same outputs.

8.1 Seroconversion Rate (SCR) and Seroprotection Rate (SPR)

The percentage of participants with seroconversion (SCR) and seroprotection (SPR) will be calculated along with Clopper-Pearson exact two-sided CIs by intervention group, age group, and post-baseline visit. For Day 43 only, the CIs will be 99.17% for the antigen/adjuvant groups and will allow testing of the statistical hypotheses. For Day 1 (SPR only) and Day 22 (SCR and SPR) and Placebo (including Day 43), the CIs will be 95% and are provided for descriptive purposes only.

The SCR and SPR will be analyzed for H7N9 HI antibody titer only.

8.2 Geometric Mean Titer

Titer results are not normally distributed so summary statistics will be calculated using log-transformed titer results. The anti-logarithm of the summary statistics will be presented. Titer results will be summarized by study group, age group, visit. Missing titer results and results below the cut-off will be handled as described in Section 4.5.

In addition, the distribution of antibody titers for each intervention group and age group will be displayed using reverse cumulative distribution curves. The x-axis of the reverse cumulative distribution curves will be presented on a log scale. A reference line will be included to show the cut-off. All study groups for a single visit will be displayed on the same page, and visits will be displayed on separate pages.

Summaries will include the number of participants with non-missing titer results, GMT, geometric standard deviation (GSD), 95% CI for GMT, minimum and maximum.

GMT will be calculated as the anti-logarithm of the mean of the log-transformed titer values i.e. anti-logarithm of $\sum(log_{10}(titer))/n$ where n is the number of participants with non-missing titer results. GSD will be calculated as the anti-logarithm of the standard deviation (SD) of the log-transformed data. The 95% CI for GMT will be calculated as the anti-logarithm of the endpoints of the 95% CI for the mean of the log-transformed data. The anti-logarithm is calculated as 10^x where x is the statistic of interest calculated from the log-transformed data (e.g. mean, SD, 95% CI endpoints).

No adjustment will be made for multiplicity in GMT and CIs are provided for descriptive purposes only. The GMT will be analyzed for both H7N9 HI and MN antibody titers.

8.3 Mean Geometric Increases (MGIs)

MGI for HI will be summarized by study group, age group, and post-baseline visit. Missing titer results and results below the cut-off will be handled as described in Section 4.5.

MGI will be calculated as the anti-logarithm of the mean of the change from baseline of log-transformed titer values at Post-Baseline and Baseline i.e. anti-logarithm of $\sum(log_{10}(titer_{Post-Baseline\ AVISIT}) - log_{10}(titer_{Baseline}))/n$ where n is the number of participants with non-missing titer results at Baseline and Post-Baseline AVISIT.

Summaries will include the number of participants with non-missing titer results at each post-baseline AVISIT, MGI, GSD of the difference in log-transformed titer results at post-baseline AVISIT and Baseline, 95% CI for MGI, minimum and maximum.

GSD will be calculated as the anti-logarithm of the SD of the change from baseline of the log-transformed data. The 95% CI for MGI will be calculated as the anti-logarithm of the endpoints of the 95% CI for the mean MGI. The anti-logarithm is calculated as 10^x where x is the statistic of interest calculated from the log-transformed data (e.g. mean, SD, 95% CI endpoints).

No adjustment will be made for multiplicity in MGI and CIs are provided for descriptive purposes only. The MGI will be analyzed for H7N9 HI antibody titers only.

8.4 Seropositivity

The percentage of seropositive participants for HI and MN as well as the associated Clopper-Pearson exact 2-sided 95% CIs will be computed by study group, age group and visit.

No adjustment will be made for multiplicity in seropositivity and CIs are provided for descriptive purposes only. Seropositivity will be analyzed for both H7N9 HI and MN antibody titers.

8.4.1 Vaccine Response Rate (VRR)

The VRR for MN as well as the associated Clopper-Pearson exact 2-sided 95% CIs will be computed by study group, age group and post-baseline visit.

No adjustment will be made for multiplicity in VRR and CIs are provided for descriptive purposes only. The VRR will be analyzed for H7N9 MN antibody titers only.

9 Safety Analysis

Safety summaries and listings will be based on the Exposed Set.

9.1 Adverse Events

Solicited events, unsolicited AEs, SAEs, medically attended AEs, AEs leading to withdrawal from intervention or from the study, and pIMDs that occur post-vaccination will be summarized and also presented in listings. AEs occurring prior to a participant receiving any study vaccine will be listed only.

The definitions for SAEs and medically attended AEs can be found in protocol sections 10.3.2 and 10.3.9.3 respectively. Further information about pIMDs can be found in protocol section 10.3.5.1.

Incomplete onset dates and end dates for any AEs will be imputed to determine if the event occurred within the time period specified for AE summaries that are described in sections 0 and 9.1.2. Actual dates recorded will be presented in listings, imputed dates will not be presented. Incomplete dates will be imputed as follows:

Missing onset dates (where UK and UKN indicate unknown or missing day and month respectively):

- If the response to "If exact start date is unknown, or is on the same day as any study vaccination, please confirm whether it occurred before or after vaccination:" is "After vaccination 1" or "After vaccination 2" then assume the start date is the date of the first and second dose of study vaccine, respectively.
- If the response is "Before vaccination" assume the following:
    - UK-MMM-YYYY: If the month and year are different from the month and year of the first dose of study vaccine, assume 01-MMM-YYYY. If the month and year are the same as the first dose of study vaccine month and year, and the end date (after any imputation) is on or after the first dose of study vaccine, then assume the date of the first dose of study vaccine. If the month and year are the same as the first dose of study vaccine month, and year and the end date (after any imputation) is prior to the first dose of study vaccine, then assume the end date for the onset date.
    - DD-UKN-YYYY/UK-UKN-YYYY: If the year is before the year of first dose of study vaccine, assume DD-JAN-YYYY/01-JAN-YYYY of the collected year. If the year is after the first dose and the same as the second dose, assume DD-JAN-YYYY/01-JAN-YYYY. If the year is the same as the first dose of study vaccine year, and the end date (after any imputation) is on or after the first dose of study vaccine, then assume the date of the first dose of study vaccine. If the year is the same as the first dose of study vaccine, and the end date (after any imputation) is prior to the first dose of study vaccine, then assume the end date for the onset date.

Missing end dates (where UK and UKN indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: Assume the last day of the month.
- DD-UKN-YYYY: Assume DD-DEC-YYYY.
- UK-UKN-YYYY: Assume 31-DEC-YYYY.

9.1.1 Solicited Events

The term "reactogenicity" refers to solicited signs and symptoms ("solicited events") occurring in the hours and days following a vaccination. Participants will be assessed for reactogenicity, to be collected for 7 days following each vaccination (the day of vaccination and the following 6 days), using a paper diary (pDiary). Solicited events will be recorded in the eDiary for the periods Day 1 to Day 7 and Day 22 to Day 28.

Solicited administration site events

Solicited administration site events for this study are pain, redness, and swelling. Solicited administration site events will be recorded according to the vaccine that was administered most recently.

Solicited systemic events

Solicited systemic events for this study are fatigue, fever, nausea, vomiting, diarrhea, abdominal pain, headache, muscle ache, joint pain, shivering (chills), sweating. The preferred location for measuring temperature in this study is oral. Solicited events will be summarized according to the defined severity grading scales in Table 10. Fever will be considered as a body temperature value ≥38°C.

Table 10 Solicited Event Intensity Grades

Adults (≥18 years)		
Event	**Intensity grade**	**Parameter**
Pain at administration site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities.
	2	Moderate: Painful when limb is moved and interferes with every day activities.
	3	Severe: Significant pain at rest. Prevents normal every day 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	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 °F**

*** Refer to the Protocol Schedule of Assessments for the definition of fever and the preferred location for temperature measurement.**

The maximum intensity of local injection site redness/swelling will be scored at GSK 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 at GSK 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)

1. Participants with solicited events will be counted based on actual intervention received for each study group and age group. Solicited events will also be presented by individual vaccine received (dose 1 and dose 2). The following categories will be included in the summary table for solicited events and will be generated on subjects who has filled in solicited symptom in the eDiary: Participants who experienced any solicited event within 7 days of vaccination
2. Participants who experienced any systemic solicited event within 7 days of vaccination
3. Participants who experienced any administration site solicited event within 7 days of vaccination

A summary table containing the number and percentage of participants showing the occurrence of any solicited event will be presented by study group, age group, visit, and timepoint. The duration of solicited events will also be summarized by study group, age group and vaccination.

The duration (in days) of a solicited event will be calculated as:

> Date of last report of a solicited event after the respective vaccination administration date within 7 days of vaccination – date of first report of a solicited event after the respective vaccination administration date + 1

The duration (in days) of an ongoing solicited event after the 7 days of vaccination will be calculated as:

> Date of last report of a solicited event after the respective vaccination administration date – date of first report of a solicited event after the respective vaccination administration date + 1

A similar calculation will be made for the second vaccination. Duration will be calculated for each solicited event separately.

A summary table for duration of solicited events within 7 days post-vaccination and a frequency table of solicited event after the 7 days of vaccination will be presented.

The number and percentage of participants experiencing each solicited event will be presented for each symptom maximal severity (defined in Table 10) by study group, age group, visit, and time point. If a solicited event occurs more than once for a participant within a time point, it will be counted in the summary only once, according to the maximal severity.

Solicited events will be listed.

9.1.2 Unsolicited Adverse Events

An unsolicited AE is an AE that was not solicited using a participant Diary and that was spontaneously communicated by the participants or a solicited administration site or systemic event that meets the criteria described in Section 0. Solicited events lasting more than 7 days after vaccination (including the day of vaccination) are also recorded as unsolicited AEs.

The original verbatim terms used by investigators to identify AEs in the Adverse Events page of the eCRF will be mapped to preferred terms (PT) using MedDRA, version to be delineated in the CSR. The AEs will then be grouped by MedDRA according to system organ class (SOC).

The following summaries will present the event count, number and percentage of participants reporting each AE and will be presented by SOC, PT, and maximum relationship to study intervention for each study group, grouped by 21 days post-vaccination at any visit and then by 2 time points (at the final analysis): 21 days post-vaccination at Visit 1, and 21 days post-vaccination at Visit 2:

- Any unsolicited AE
- Any severe unsolicited AE (grade 3)
- Any related unsolicited AE
- Any severe related unsolicited AE (grade 3 related)
- Unsolicited MAEs
- Any AEs with MAEs
- Any related AEs with MAEs

Additional summaries will present the number and percentage of participants reporting AEs in the following categories and will be presented by SOC and PT for each study group and age group from Day 1 through the Day 43 visit and from Day 1 through the end of study:

- SAEs
- AEs leading to withdrawal from study drug (through Day 22 only
- AEs leading to withdrawal from study
- MAEs (within 21 days post each vaccination)
- pIMDs

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

Missing data will be handled as described in Section 4.5.

9.2 COVID-19 Assessments

Frequencies and percentages of participants with suspected, probable, or confirmed COVID-19 cases will be summarized for the Exposed Set for each study group, age group, and overall.

In addition, a summary of the following COVID-19 additional assessments will be produced on all assessments reported. with the denominator being subject (i.e. if more than one per subject, counted only once):

- Does the subject have a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset?
- Did the subject visit any health care facility in the 14 days prior to symptom onset?
- Did the subject have contact with a confirmed or probable case in the 14 days prior to symptom onset?
- Were any concomitant medications taken by the subject, including experimental medications, to treat COVID-19?

Additional COVID-19 case details will be produced. The listing will include:

- Site Identifier
- Treatment
- Period
- Unique Subject Identifier
- Subject Identifier

- COVID-19 case diagnosis
- COVID-19 test performed
- Result of the COVID-19 test
- Assessments and Symptom Assessments performed
- Results of the Assessments and Symptom Assessments

Participants with COVID-19 cases or who take COVID-19 vaccine may be excluded from the per protocol analysis depending on timing of the infection or the vaccination. For example, if a participant has COVID-19 infection between Day 22 and Day 43, the participant may be excluded from analysis of Day 43 data but still be included in the analysis for Day 22 data.

The COVID-19 related protocol deviations (e.g. blood draw outside of allowed time window due to COVID-19 related restrictions of movement) will be reviewed together with other protocol deviations. Participants with major protocol deviations may be excluded from per protocol analysis sets, as described in Section 5.2.

If study procedures are modified due to special circumstances, there may be a requirement to conduct analyses that separately describe the data collected during the period of modified study procedures. If required, these analyses will be described in a separate analysis plan.

9.3 Clinical Laboratory Evaluations

Clinical laboratory measurements (e.g. clinical chemistry, hematology, and urinalysis) are not scheduled to be taken during the study; however, clinical laboratory tests may be done 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.

Should any clinical laboratory tests be performed during the study for a participant, abnormal laboratory findings or other abnormal assessments that are judged by the investigator to be clinically significant will be recorded as an AE or SAE if they meet the definition of an AE or SAE and will be included in AE/SAE summaries.

9.4 Physical Examination and Vital Signs

At a minimum, temperature and vital signs (e.g. heart rate and respiratory rate, blood pressure) must be collected. Participants will undergo a physical examination and vital signs are to be taken prior to the first vaccination and will consist of 1 pulse and 1 blood pressure measurement. Blood pressure and pulse measurements will be assessed by a completely automated device on Day 1 only. Manual techniques will be used only if an automated device is not available. Collected information will be recorded in the eCRF. Blood pressure and pulse measurements will be listed only.

Summary statistics (mean, SD, minimum and maximum) for pre-vaccination body temperature at each visit will be presented by study group and age group for the Exposed Set. Pre-vaccination vital signs and body temperature will be listed for the Exposed Set.

9.5 Pregnancy

Female participants of childbearing potential will have a urine pregnancy test prior to any study vaccine(s) administration.

Pregnancy test results will be displayed in a listing for the Exposed Set. Listings of pregnancy will also be generated.

10 Sequence of Analyses

10.1 iSRC Review

At least 2 iSRC reviews are planned, as described in Section 3.1. For each iSRC review, a subset of unblinded Tables, Listings and Figures (TLFs) from the main analysis will be generated by PPD and delivered to the iSRC team at GSK for their review. The TLFs required for these reviews are detailed separately in the TLF Table of Contents (ToC). Details regarding the timing and scope of iSRC reviews will be provided in the iSRC charter.

The iSRC will review the following data:

1. Participant demographic data
2. Adverse Events (AEs) / Serious Adverse Events (SAEs), including Council for International Organizations of Medical Sciences (CIOMS) reports, including listings for:
    - All AEs
    - Potential immune-mediated diseases (pIMDs)

- Fatal SAEs
- AEs/SAEs/pIMDs leading to permanent discontinuation from study treatment or withdrawal from the study
- AE/SAEs/pIMDs causally related to study vaccine

3. Participant Disposition listing (number of subjects vaccinated, withdrew from the study, withdrawal reasons)

4. Other information as deemed necessary by the study team/iSRC

The Safety Review Team (SRT) will review the same safety data, but in a blinded manner.

10.2 Analysis at Day 43

An interim analysis will be performed on data collected through the Day 43 visit. This interim analysis will provide intervention-level unblinded summaries for GSK, Biomedical Advanced Research and Development Authority, and regulatory agency review, and no individual unblinding data will be provided.

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

- Analyses of cleaned immunogenicity data through the Day 43 visit will be conducted.
- Analyses of cleaned solicited administration site events and solicited systemic events data collected during a 7-day follow-up period (Day 1 to Day 7) after each vaccination will be conducted.
- Analyses of unsolicited AEs and MAEs up to 21 days post each vaccination presented overall per subject on as clean as possible data.
- Analyses of SAEs, pIMDs, pregnancies and withdrawals due to AEs collected up to the Day 43 post-vaccination visit will be carried out.
- Blinded listing of pregnancies and withdrawals due to AEs collected up to the Day 43 post-vaccination visit will be presented.
- Results will be presented in a Day 43 statistical report. Access to individual intervention codes will be restricted to the designated unblinded 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 Month 13 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 Month 13. All final data will be presented in the listings provided at Month 13.

10.3 Final Analysis at Month 13

A final data analysis will be performed at the end of study (Month 13) of all primary and secondary endpoints based on the clean data, including evaluations of:

- Immunogenicity at all measured time points (Days 1, 22 and 43).
- Solicited administration site events and solicited systemic events data reported 7 days after each vaccination (Day 1 to Day 7 and Day 22 to Day 28).
- Unsolicited AEs and MAEs reported up to 21 days after each vaccination.
- Concomitant medications reported up to 21 days after each vaccination.
- SAEs, pIMDs and withdrawals due to AEs collected throughout the entire study.
- Pregnancies throughout the entire study.

An integrated CSR containing all data will be written and made available to the investigators.

10.4 Statistical Considerations for the Analysis at Day 43

Since the primary immunogenicity endpoints for the study will be complete by the Day 43 visit (collection past Day 43 includes only assessments for unsolicited AEs leading to study withdrawal, SAEs and pIMDs), 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 5% (two-sided intervals) and a Bonferroni adjustment will be applied to allow simultaneous multiple comparisons of each antigen/adjuvant group. No further adjustment is needed since sequential testing will be used for each antigen/adjuvant group related to the two endpoints and to the two age categories. For the secondary immunogenicity and primary safety analyses no adjustment for multiple comparisons will be made in each antigen/adjuvant group as the CIs are provided for descriptive purposes only. No adjustment is applied for the Placebo group.

11 Changes to the Protocol Planned Analysis

The duration of solicited events will also be summarized by study group, age group and vaccination.

12 References

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13 Appendices

13.1 Schedule of Study Events

Table 11 List of Study Procedures

	Primary					Follow-up			
Type of contact	**Visit 1**	**TC1**	**Visit 2**	**TC2**	**Visit 3**	**TC3**	**TC4**	**TC5**	**TC6**
Time points	**Day 1**	**Day 8**	**Day 22**	**Day 29**	**Day 43**				
Sampling time points	**Pre-Vacc I**		**Pre-Vacc II**		**Post-Vacc II**	**Month 4**	**Month 7**	**Month 10**	**Month 13**
Informed consent	●								
Check inclusion/exclusion criteria	●								
Collect demographic data	●								
Vaccine/Product									
Study group and intervention number allocation	O								
Intervention number allocation for subsequent dose			O						
Recording of administered intervention number	●		●						
Vaccine administration	●		●						
Clinical specimens for laboratory assays									
Blood sampling for antibody determination (25 mL)	●		●		●				
Safety assessments									
Medical history[1]	●								
Physical examination[2]	●								
History of administration of adjuvanted vaccine and influenza vaccine	●								
Urine pregnancy test[3]	●		●						
Check warnings and precautions to vaccination	●		●						
Pre-vaccination body temperature[4]	●		●						
Record any concomitant medication/vaccination	●		●		●				
Distribution of diary cards and COVID-19 assessment cards[5]	O		O						

	Primary					Follow-up			
Type of contact	**Visit 1**	**TC1**	**Visit 2**	**TC2**	**Visit 3**	**TC3**	**TC4**	**TC5**	**TC6**
Time points	**Day 1**	**Day 8**	**Day 22**	**Day 29**	**Day 43**				
Sampling time points	**Pre-Vacc I**		**Pre-Vacc II**		**Post-Vacc II**	**Month 4**	**Month 7**	**Month 10**	**Month 13**
Telephone contact		●		●		●	●	●	●
Recording of solicited administration site and systemic events (Days 1-7 after each vaccination)[6]	●		●						
Recording of unsolicited adverse events and MAEs (Days 1-21 after each vaccination)[6]	●	●	●	●	●				
Occurrence of urticaria/rash within 30 minutes post-vaccination observation	●		●						
Return of diary cards and COVID-19 assessment cards[5]			O		O				
Diary card transcription by investigator or delegate[6]			●		●				
Reporting of pIMDs	●	●	●	●	●	●	●	●	●
Reporting of SAEs, pregnancies	●	●	●	●	●	●	●	●	●
Study Conclusion									●

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

Note: Participants who discontinue or withdraw from the study should be followed with telephone contacts at Months 4, 7, 10, and 13 (as applicable) for safety follow-up.

MAEs: medically attended adverse events; Pre-Vacc: pre-vaccination; pIMDs: potential immune-mediated diseases; Post-Vacc: post-vaccination; SAEs: serious adverse events; TC: telephone contact

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

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

1. Medical history data should include the presence or absence of risk factors for complications associated with influenza. Influenza vaccination history covers influenza vaccines administered in the previous 3 influenza seasons (if any). Clinically significant abnormalities are to be captured in the eCRF as adverse events.
2. At a minimum, temperature and vital signs (e.g. heart rate and respiratory rate, blood pressure) must be collected.
3. Urine pregnancy test to be performed for women of child-bearing potential; a negative result must be obtained prior to each vaccination.
4. Fever is defined as temperature ≥ 38.0°C/100.4°F. The preferred location 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 and/or vaccinated at the discretion of the investigator.
5. Diary cards used to capture both solicited administration site and systemic events (Days 1-7 after each vaccination) and unsolicited adverse events (Days 1-21 after each vaccination) and COVID-19 assessment cards are provided at the time of each vaccination and collected at the next visit following each vaccination

(solicited administration site and systemic events portion of card) and at the subsequent visit (unsolicited adverse events portion of card) or by mail using the pre-stamped envelope received at the site.

6. Participant records intensity and duration of solicited administration site events and occurrence, intensity and duration, of each solicited systemic event and unsolicited adverse event. Investigator or delegate later assesses and records relationship of each solicited administration site and systemic event and unsolicited adverse event to vaccination.