Protocol

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

NCT ID: NCT04789577

Date of Document: 22 February 2022

Clinical Study Protocol
Sponsor:
GlaxoSmithKline Biologicals SA
Rue de l'Institut 89
1330 Rixensart, Belgium

Primary Study vaccine/product and number	GlaxoSmithKline Biologicals' Influenza A/Hong Kong/125/2017-like (H7N9) virus vaccine: GSK3206641A (Q-PAN H7N9 vaccine adjuvanted with AS03)
Other Study vaccine/product	Placebo
eTrack study number and abbreviated title	209671 (FLU Q-PAN H7N9=AS03-002)
Date of protocol	Final: 13 February 2020
Date of protocol amendment	Amendment 1 Final: 27 August 2020 Amendment 2 Final: 22 February 2022
Title	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
Short title	An observer-blind study to evaluate the safety and immunogenicity of GlaxoSmithKline Biologicals' influenza vaccine GSK3206641A administered in adults 18 to 64 years of age and 65 years of age and older
IND number	015763

Based on GSK Biologicals' Protocol WS v17.0

Protocol Amendment 2 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	209671 (FLU Q-PAN H7N9=AS03-002)
Date of protocol amendment	Amendment 2 Final: 22 February 2022
Title	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
Sponsor signatory	***Andrew Hastie***, Clinical and Epidemiology Project Lead, Vaccines for Influenza **(Amended 22 February 2022)**
Signature	_____
Date	_____

Protocol Amendment 2 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments or protocol administrative changes, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline Biologicals SA (GSK).
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the GSK study vaccine and other study-related duties and functions as described in the protocol.
- To supervise any individual or party to whom I have delegated trial-related duties and functions conducted at the trial site.
- To ensure that any individual or party to whom I have delegated trial-related duties and functions conducted at the trial site are qualified to perform those trial-related duties and functions.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK and the express written informed consent of the participant and/or the participant's legally acceptable representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To co-operate with a representatives of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- To have control of all essential documents and records generated under my responsibility before, during, and after the trial.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational vaccine, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information for the solely for the purpose of complying with regulatory requirements.

Hence, I:

- Agree to supply GSK with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
- Agree that GSK may disclose any information about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

eTrack study number and Abbreviated Title	209671 (FLU Q-PAN H7N9=AS03-002)
Date of protocol amendment	Amendment 2 Final: 22 February 2022
Title	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
Investigator name	_____
Signature	_____
Date	_____

Sponsor Information

1. Sponsor

GlaxoSmithKline Biologicals SA
Rue de l'Institut 89
1330 Rixensart, Belgium

2. Sponsor Medical Expert for the Study

Refer to the local study contact information document.

3. Sponsor Study Monitor

Refer to the local study contact information document.

4. Sponsor Study Contact for Reporting of a Serious Adverse Event

Central Back-up Study Contact for Reporting SAEs: refer to the protocol Section 8.3.3.1.

Study Contact for Reporting SAEs: refer to the local study contact information document.

5. Details for Emergency Unblinding

Refer to the protocol Section 6.3.5.1.

This project has been funded in whole or in part with Federal funds from the Department of Health and Human Services; Office of the Assistant Secretary for Preparedness and Response; Biomedical Advanced Research and Development Authority, under Contract No. HHSO100201600004I.

BARDA Number CLIN 0013

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document history

Document	Date
Amendment 2	22 February 2022
Amendment 1	27 August 2020
Original Protocol	13 February 2020

Amendment 2 22 February 2022

Overall Rationale for the Amendment:

Additional analysis sets (modified per protocol sets) have been defined to incorporate individuals with extended intervals between vaccination Visit 1 (Day 1) and Visit 2 (Day 22), and between Visit 2 (Day 22) and Visit 3 (Day 43).

These analysis sets are included because of the observation of a higher than anticipated number of out of window visits impacting the per protocol sets (PPS).

Additionally, aligned with current document standards, the timeframe for reporting of pregnancies by the investigator to the sponsor was updated from 2 weeks to 24 hours, and the list of potential immune-mediated disease (pIMDs) was updated.

Updates regarding study endpoints and planned analyses were made for clarity.

List of main changes in the protocol and their rationale

Section # and Name	Description of Change	Brief Rationale
8.3.3 Regulatory reporting requirements for SAEs, pregnancies, and other events	In Table 12, the timeframe for reporting pregnancies for Initial Reports and Follow-up of Relevant Information on a Previous Report was modified to: ***24 hours***	Updated to match current document standards.
9.3 Population for Analyses	The following text was added to Table 16: ***Modified PPS (mPPS) 1: The mPPS 1 is a subset of FAS 1. The mPPS 1 includes all FAS 1 participants with no major protocol deviations that led 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 between 18-32 study days. The interval between Visit 2 and Visit 3 will be 14-32 calendar days.*** ***Major protocol deviations leading to exclusion will be defined in the Statistical Analysis Plan (SAP) and the Study Deviation Rules Document and will be***	Additional analysis sets have been defined to incorporate individuals with extended intervals between vaccination Visit 1 (Day 1) and Visit 2 (Day 22), and between Visit 2 (Day 22) and Visit 3 (Day 43). These analysis sets are included because of the observation of a higher than anticipated number of out of window visits impacting the per protocol sets.

Section # and Name	Description of Change	Brief Rationale
	finalized prior to the interim analysis defined in Section 9.5. ***mPPS 2: 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 between 18-32 study days.*** ***Major protocol deviations leading to exclusion will be defined in the SAP and the Study Deviation Rules document and will be finalized prior to the interim analysis defined in Section 9.5.*** ***MN mPPS 1: All participants in the MN Set who are also part of the mPPS 1.*** ***MN mPPS 2: All participants in the MN Set who are also part of the mPPS 2.***	
9.4.1 General Considerations	The following text was modified as follows: – The primary and secondary HI immunogenicity analyses will be based on the ***applicable*** Per Protocol Set (PPS) ***as described in Section 9.3 (Table 16). Supplementary analyses for primary and secondary HI immunogenicity analyses will be based on the applicable mPPS.*** If the difference between PPS ***1*** and FAS ***1*** is greater than 10%, a second analysis based on the FAS will be performed to complement the PPS analysis. – The MN immunogenicity analyses will be based on the ***applicable*** Microneutralization Per Protocol Set (MNPPS) ***as described in Section 9.3 (Table 16)***. ***Supplementary analyses for MN immunogenicity analyses will be based on the applicable MN mPPS.***	Additional analysis sets have been defined to incorporate individuals with extended intervals between vaccination Visit 1 (Day 1) and Visit 2 (Day 22), and between Visit 2 (Day 22) and Visit 3 (Day 43). These analysis sets are included because of the observation of a higher than anticipated number of out of window visits impacting the per protocol sets. Few editorial changes were made for clarity.

Section # and Name	Description of Change	Brief Rationale
9.4.2 Participants disposition	The following text was modified as follows: Major deviations will be summarized for the Exposed Set (ES) for each study group, age group, and overall. The reason for elimination from the PPS 1 and PPS 2 ***and mPPS 1 and mPPS 2*** will also be summarized. ***The same will be done for MNPPS 1, MNPPS 2, MN mPPS 1 and MN mPPS 2.***	Additional analysis sets have been defined to incorporate individuals with extended intervals between vaccination Visit 1 (Day 1) and Visit 2 (Day 22), and between Visit 2 (Day 22) and Visit 3 (Day 43). These analysis sets are included because of the observation of a higher than anticipated number of out of window visits impacting the per protocol sets.
9.4.3.1 Immunogenicity	The following text was added: ***Supplementary immunogenicity analyses will be based on the mPPS 1 set.***	Additional analysis sets have been defined to incorporate individuals with extended intervals between vaccination Visit 1 (Day 1) and Visit 2 (Day 22), and between Visit 2 (Day 22) and Visit 3 (Day 43). These analysis sets are included because of the observation of a higher than anticipated number of out of window visits impacting the per protocol sets.
9.4.3.2 Safety	The following text was modified (see Appendix 8 for deleted text): Unsolicited AE endpoints – Occurrence and relationship to vaccination of unsolicited AEs within 21 days after each vaccination. – Occurrence and relationship to vaccination of AEs with MAEs within 21 days after each vaccination.	Updates were made for clarity regarding safety endpoints.
9.4.4.1 Immunogenicity	The following text was modified: For a subset of participants (MNPPS 1 and MNPPS 2 sets ***and MN mPPS 1 and MN mPPS 2***), the following aggregate variables will be calculated for each vaccine group for vaccine-homologous H7N9 MN antibody titer:	Additional analysis sets have been defined to incorporate individuals with extended intervals between vaccination Visit 1 (Day 1) and Visit 2 (Day 22), and between Visit 2 (Day 22) and Visit 3 (Day 43). These analysis sets are included because of the observation of a higher than anticipated number of out of window visits impacting the per protocol sets.
9.4.5.1 Demography and baseline characteristics analyses	The following text was modified (see Appendix 8 for deleted text): The analysis of demographics will be performed separately for the ES and for the participants contributing to the PPS ***(and mPPS)***.	Editorial changes were made to clarify the language in this section.
9.5.1.1 Analysis at Day 43	The following text was modified regarding analyses planned at Day 43 (see Appendix 8 for deleted text): – ***Analyses of unsolicited AEs and MAEs up to 21 days after each vaccination on as clean as possible data.***	Updates were made for clarity regarding safety endpoints and related planned statistical analyses.

Section # and Name	Description of Change	Brief Rationale
	– Analyses of SAEs, pIMDs, pregnancies and withdrawals due to AEs collected up to the Day 43 post-vaccination visit will be carried out.	
9.5.1.2 Final analysis (Month 13)	The following text was modified regarding analyses planned at end of study (Month 13 (see Appendix 8 for deleted text): – Unsolicited AEs and MAEs reported up to 21 days after each vaccination. – Concomitant medications reported up to ***21 days after each vaccination.***	Updates were made for clarity regarding safety endpoints and related planned statistical analyses.
9.5.2 Statistical consideration for interim analysis	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***, ***S***AEs, 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. (see Appendix 8 for deleted text)	Updates were made for clarity regarding study endpoints and related planned statistical analyses.
10.3.5.1 Potential immune-mediated diseases	Table 19 was modified to current GSK protocol requirements	The pIMD list was updated to reflect changes following MedDRA (Medical Dictionary for Regulatory Activities) updates and also to consider emerging pIMDs of interest in the context of COVID-19 vaccine safety monitoring.
10.3.8.1 Time period for collecting and recording AEs	The following text was modified (see Appendix 8 for deleted text): All AEs that occur within 21 days following administration of each dose of study vaccine/product must be recorded into the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination-related.	Updates were made for clarity regarding safety endpoints.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Rationale:

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 [WHO, 2019; FAO, 2019]. 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 [Xiang, 2016; Zhou, 2017].

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 influenza A/Hong Kong/125/2017-like (H7N9) virus vaccine and will conduct a clinical trial in the United States (US) to assess the safety and immunogenicity of different formulations of H7N9 split virus vaccine produced in GSK's Québec facility, administered with AS03 adjuvant.

In addition, this study is also intended to capture COVID-19 cases among study participants based on the WHO criteria (suspected, probable, and confirmed cases).

Objectives and Endpoints:

Objectives and endpoints can be found in Table 3.

1.2. Schema

The study design overview can be found in Figure 1.

1.3. Schedule of Activities (SoA)

The schedule of activities can be found in Table 1.

Table 1 Schedule of Activities

	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**	**Month 4**	**Month 7**	**Month 10**	**Month 13**
Sampling time points	**Pre-Vacc I**		**Pre-Vacc II**		**Post-Vacc II**				
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[1]	●								
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 card[5]	O		O						
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 card[5]			O		O				
Diary card transcription by investigator or delegate[6]			●		●				
Reporting of pIMDs	●	●	●	●	●	●	●	●	●

	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**	**Month 4**	**Month 7**	**Month 10**	**Month 13**
Sampling time points	**Pre-Vacc I**		**Pre-Vacc II**		**Post-Vacc II**				
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.
● 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 or risk factors for complications associated with influenza. Influenza vaccination history covers influenza vaccines administered in the previous 3 influenza seasons (if any).
[2] At a minimum, temperature and vital signs (e.g. heart rate and respiratory rate, blood pressure) must be collected prior to vaccination. Clinically significant abnormalities are to be captured in the eCRF as adverse events.
[3] Urine pregnancy test to be performed for women of childbearing 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 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 occurrence, intensity, and duration of solicited administration site events and of each solicited systemic event and unsolicited adverse event. Investigator or delegate later assesses and records relationship of each unsolicited adverse event.
eCRF: electronic case report form; 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

Table 2 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 Set (PPS) for immunogenicity analysis for the specified interval if blood collections are outside this interval. Refer to Table 16 for populations for analyses.
TC: telephone contact

2. INTRODUCTION

2.1. Study rationale

Novel influenza A viruses, including subtypes H5N1, H3N2v, H9N2, A(H1N1)pdm09, and H7N9, 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.

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 WHO, including 616 deaths [WHO, 2019; FAO, 2019]. 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 [Xiang, 2016; Zhou, 2017].

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. GSK has produced an investigational AS03-adjuvanted influenza A/Hong Kong/125/2017-like (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.

2.2. Background

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 Adjuvant System 03 (AS03). This adjuvant system contains α-tocopherol (11.86 mg for "AS03A"; 5.93 mg for "AS03B") 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 influenza A/Hong Kong/125/2017-like (H7N9) virus vaccine will be evaluated.

Please refer to the current Investigator's Brochure (IB) for information regarding pre-clinical and clinical studies and the potential risks and benefits of GSK's AS03-adjuvanted pandemic influenza vaccines.

2.3. Benefit/Risk assessment

Considering the measures taken to minimize risk to participants enrolled in this study, the potential or identified risks are justified by the potential benefits (prevention) that may be afforded to participants.

Detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of GSK's AS03-adjuvanted pandemic influenza vaccines can be found in the IB.

3. OBJECTIVES AND ENDPOINTS

Table 3 Study objectives and endpoints

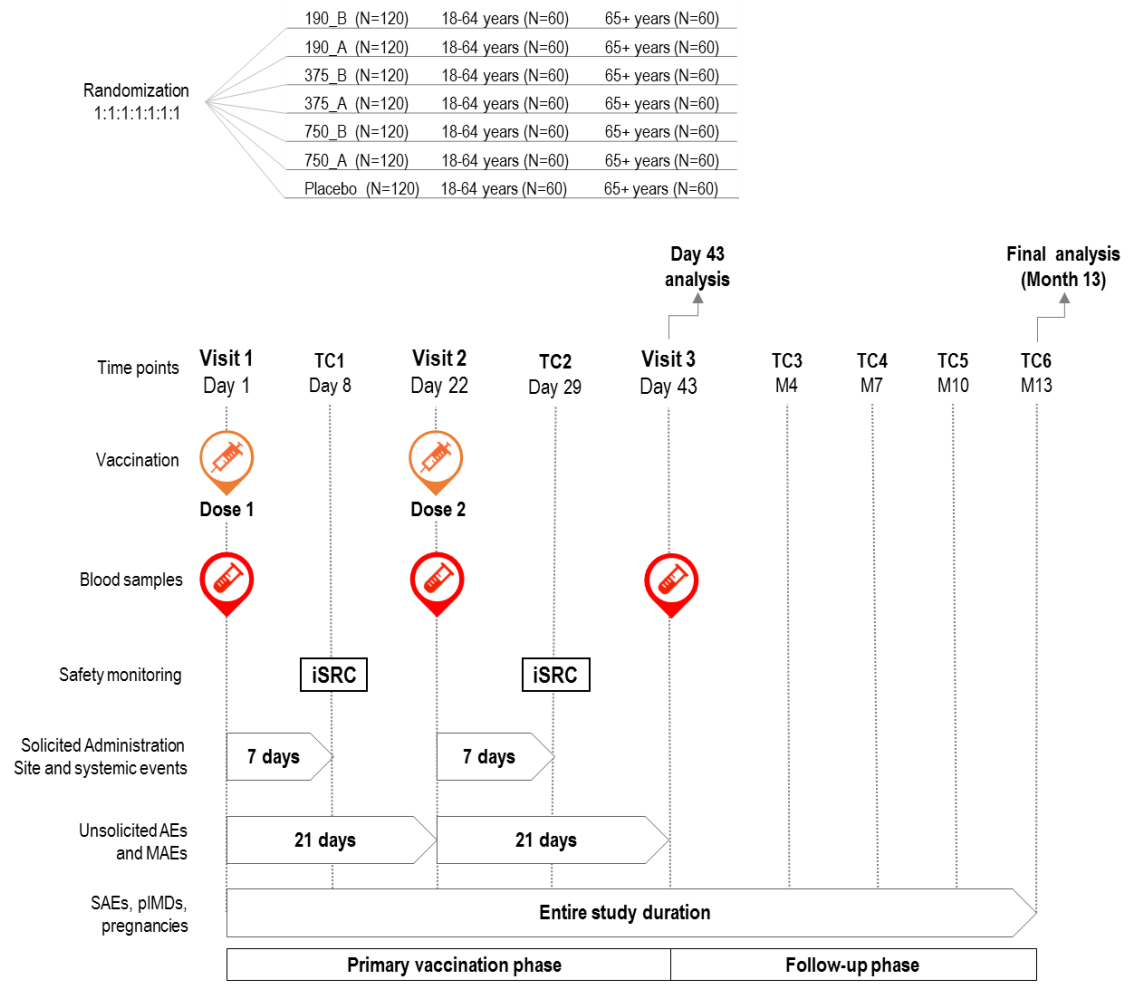
Objectives	Endpoints
Primary	
Co-primary Immunogenicity: • To evaluate whether the monovalent influenza A/Hong Kong/125/2017-like (H7N9) virus vaccine containing 1.9 µg, 3.75 µg, or 7.5 µg of hemagglutinin (HA) adjuvanted with $AS03_A$ or $AS03_B$ elicits a hemagglutination inhibition (HI) antibody response to the vaccine-homologous virus that meets or exceeds the US Food and Drug Administration, Center for Biologics Evaluation and Research immunogenicity criteria at the Day 43 visit.	• Humoral immune response in terms of vaccine-homologous HI antibody titers: – Seroprotection rates (SPR) at Day 43 – Seroconversion rates (SCR) at Day 43
Safety: • To describe the safety and reactogenicity of the different vaccine formulations through the Day 43 visit.	• Occurrence of adverse events (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 medically attended adverse events (MAEs) for 21 days after each vaccination – Serious adverse events (SAEs), potential immune-mediated disease (pIMDs) up to Day 43 visit
Safety: • To describe the safety of the different vaccine formulations through Month 13	• Occurrence of pIMDs and SAEs until Month 13
Secondary	
• To describe the vaccine homologous H7N9 HI antibody profile in all study groups at Days 1, 22, and 43	• 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 Days 22 – SPR at Days 1 and 22 – Mean Geometric Increase (MGI) at Days 22 and 43
• To describe the vaccine homologous (H7N9) Microneutralization (MN) antibody profiles in a subset of participants at Days 1, 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

See List of abbreviations and Glossary of terms for the definitions of AE, GMT, HI, MAE, MGI, MN, pIMD, SAE, SCR, SPR, and VRR.

4. STUDY DESIGN

4.1. Overall design

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 (Section 8.2.2.2).
AE: adverse event; M: Month; MAE: medically attended adverse events; N: number of participants; pIMD: potential immune-mediated disease; SAE: serious adverse event; TC: telephone contact

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 COVID-19 cases among study participants based on the WHO criteria [WHO, 2020]: 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 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.

- Type of study: self-contained.
- Experimental design: Phase I/II, observer-blind, randomized, placebo-controlled, age stratified, multi-center study with 7 parallel groups.
- Duration of study: Each participant will participate for approximately 13 months (403 days) after receipt of the initial vaccine dose.
- Control: placebo.
- Blinding: observer-blind.
- Data collection: electronic case report form (eCRF). Solicited administration site or systemic events and any unsolicited AEs will be collected using a Participant Diary (Paper Diary [pDiary]).
- Safety monitoring: Refer to Section 8.2.2 for the description of review of safety data by an internal Safety Review Committee (iSRC) and details regarding holding rules and safety monitoring.

Table 4 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 5 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		

* 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.

4.2. Scientific rationale for study design

The study will evaluate the safety and immunogenicity of H7N9 antigen (A/Hong Kong/125/2017) in combination with full or half doses of AS03 adjuvant system.

Non-adjuvanted H7 influenza antigens have been poorly immunogenic in vaccine studies to date. For this reason, GSK anticipates that an adjuvanted vaccine, administered as a two-dose series, will be required to elicit a potentially protective immune response.

The inclusion of a placebo control group in this observer-blind study will permit unbiased assessment of vaccine safety and reactogenicity.

4.3. Justification for dose

The rationale for evaluating 1.9 µg, 3.75 µg and 7.5 µg doses of H7N9 antigen is based on the Biomedical Advanced Research and Development Authority (BARDA) requirement to assess the dose-sparing ability of influenza A/Hong Kong/125/2017-like (H7N9) virus vaccine in combination with full or half doses of AS03. All 3 antigen doses have been part of GSK's clinical development program with an AS03-adjuvanted split virus H5N1 and H7N9 influenza vaccines.

$AS03_A$ (11.86 mg tocopherol in 0.25 mL) and $AS03_B$ (5.93 mg tocopherol in 0.125 mL) will be evaluated in this study, since both AS03 formulations have been shown to improve the immunogenicity of inactivated split-virion H5N1 and H7N9 influenza vaccines in studies conducted by GSK.

4.4. End of Study definition

A participant is considered to have completed the study if he/she is available for the last scheduled contact at Month 13 as described in the protocol.

End of Study: Last subject last visit (telephone contact at Month 13).

5. STUDY POPULATION

5.1. Inclusion criteria for enrollment

Adherence to these criteria as specified in the protocol is essential. Inclusion criteria deviations are not allowed because they can jeopardize the scientific integrity or regulatory acceptability of the study or participant safety.

All participants must satisfy ALL of the following criteria at study entry:

1. Healthy participants as established by medical history and clinical examination before entering into the study.
2. A male or female ≥ 18 years of age at the time of first vaccination.
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 and COVID-19 assessment card, return for follow-up visits, or return the diary cards and COVID-19 assessment card in a timely manner using the pre-stamped envelope received at the site).
4. Written or witnessed/thumb printed informed consent obtained from the participant prior to performance of any study specific procedure.
5. Female participants of non-childbearing potential may be enrolled in the study. Non-childbearing potential is defined as pre-menarche, current bilateral tubal ligation or occlusion hysterectomy, bilateral ovariectomy or post-menopause.

Female participants of childbearing potential may be enrolled in the study, if the participant:

- has practiced adequate contraception for 1 month prior to vaccination, and
- has a negative pregnancy test on the day of vaccination, and
- has agreed to continue adequate contraception during the entire treatment period and for 2 months after completion of the vaccination series.

Refer to Section 10.5.1 for definitions of women of childbearing potential and adequate contraception.

5.2. Exclusion criteria for enrollment

Adherence to criteria specified in the protocol is essential. Exclusion criteria deviations are not allowed because they can potentially jeopardize the scientific integrity or regulatory acceptability of the study or safety of the participant.

The following criteria should be checked at the time of study entry. The potential participant MUST NOT be included in the study if ANY exclusion criterion applies:

5.2.1. Medical conditions

1. Current diagnosis or history of autoimmune disorder(s). Refer to Table 19 for conditions that constitute autoimmune disorder(s).
2. History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine.
3. Hypersensitivity to latex.
4. Acute or chronic clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality that appears uncontrolled, as determined by history or physical examination.
5. Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
6. Recurrent history or uncontrolled neurological disorders or seizures.
7. History of Guillain-Barré syndrome.
8. Diagnosed with narcolepsy; or history of narcolepsy in a participant's parent, sibling or child.
9. 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 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.
10. Documented human immunodeficiency virus-positive participant.
11. Any clinically significant* hematological laboratory abnormality.

    *The investigator should use his/her clinical judgement to decide which abnormalities are clinically significant.
12. Bedridden participants.
13. 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

1. Use of any investigational or non-registered product (drug, vaccine or medical device) other than the study vaccine/product during the period beginning 30 days before the first dose of study vaccine/product (Day -29 to Day 1), or planned use during the study period.
2. Administration of long-acting immune-modifying drugs at any time during the study period (e.g. infliximab).
3. Administration of immunoglobulins and/or any blood products or plasma derivatives during the period starting 3 months before the first dose of study vaccine/product or planned administration during the study period.
4. 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/product dose. For corticosteroids, this will mean prednisone equivalent ≥ 20 mg/day. Inhaled and topical steroids are allowed.

5.2.3. Prior/Concurrent clinical study experience

1. 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).

5.2.4. Other exclusions

1. Pregnant or lactating female.
2. Female planning to become pregnant or planning to discontinue contraceptive precautions within 2 months after completion of the vaccination series.
3. History of or current chronic alcohol consumption and/or drug abuse.
4. 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. Any study personnel or immediate dependents, family, or household member.

5.3. Lifestyle considerations

Not applicable

5.4. Screen failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention.

6. STUDY INTERVENTION

A 'study intervention' is defined as a set of investigational or marketed product(s) or placebo intended to be administered to a participant during the study.

Refer to the Study Procedures Manual (SPM) for additional details.

6.1. Study intervention(s) administered

Dose preparation is to be performed by an unblinded member of the site staff. For study vaccines adjuvanted with AS03, thorough mixing of the antigen and adjuvant components is required. Placebo does not require mixing. Detailed instructions for vaccine and placebo preparation will be provided separately in the SPM.

All vials of vaccine/product provided in this study are intended for single use only.

All used vials will be retained for monitoring and reconciliation purposes.

All doses are administered intramuscularly into the deltoid region of the non-dominant arm. All study vaccines will be administered by an unblinded member of the site staff who may also participate in dose preparation, but who is barred from participation in any other study functions and may not contribute any observations.

The needle for any intramuscular injection should be long enough to reach the muscle mass and prevent vaccine from seeping into subcutaneous tissue, but not so long as to involve underlying nerves and blood vessels or bone. Vaccinators should be familiar with the anatomy of the area into which they are injecting vaccine.

A summary of the study interventions can be found in Table 6. The schedule of study intervention administration can be found in Section 4.

Table 6 Study interventions administered

Study Intervention Name:	**1.9 µg HA + AS03B ****		**1.9 µg HA + AS03A ***		**3.75 µg HA + AS03B ****		**3.75 µg HA + AS03A ***	
Vaccine/Product name:	FLU-Q-PAN H7N9 (1.9)	AS03B	FLU-Q-PAN H7N9 (1.9)	AS03A	FLU-Q-PAN H7N9 (3.75)	AS03B	FLU-Q-PAN H7N9 (3.75)	AS03A
Presentation:	Suspension for suspension for injection in vial	Emulsion for suspension for injection in vial	Suspension for suspension for injection in vial	Emulsion for suspension for injection in vial	Suspension for suspension for injection in vial	Emulsion for suspension for injection in vial	Suspension for suspension for injection in vial	Emulsion for suspension for injection in vial
Vaccine/product formulation:	A/Hong Kong/125/2017 - like (H7N9) (1.9 µg HA); Water for injections q.s. 0.125 mL	AS03B: DL-α-tocopherol and squalene in an o/w emulsion (5.93 mg DL-α-tocopherol); Water for injections q.s. 0.125 mL	A/Hong Kong/125/2017 - like (H7N9) (1.9 µg HA); Water for injections q.s. 0.125 mL	AS03A: DL-α-tocopherol and squalene in an o/w emulsion (11.86 mg DL-α-tocopherol); Water for injections q.s. 0.25 mL	A/Hong Kong/125/2017 - like (H7N9) (3.75 µg HA); Water for injections q.s. 0.125 mL	AS03B: DL-α-tocopherol and squalene in an o/w emulsion (5.93 mg DL-α-tocopherol); Water for injections q.s. 0.125 mL	A/Hong Kong/125/2017 - like (H7N9) (3.75 µg HA); Water for injections q.s. 0.25 mL	AS03A: DL-α-tocopherol and squalene in an o/w emulsion (11.86 mg DL-α-tocopherol); Water for injections q.s. 0.25 mL
Volume to be administered:	0.25 milliliter(s)		0.375 milliliter(s)		0.25 milliliter(s)		0.5 milliliter(s)	
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 Labelling:	Refer to the Standard Procedures Manual for more details							
Manufacturer:	GSK Biologicals SA							
Type of contact/ Time points:	Visit 1 (Day 1), Visit 2 (Day 22)							

Study Intervention Name:	**7.5 µg HA + AS03B ****		**7.5 µg HA + AS03A ***		**Placebo**
Vaccine/Product name:	FLU-Q-PAN H7N9 (7.5)	AS03B	FLU-Q-PAN H7N9 (7.5)	AS03A	Formulation buffer S9b ***
Presentation:	Suspension for suspension for injection in vial	Emulsion for suspension for injection in vial	Suspension for suspension for injection in vial	Emulsion for suspension for injection in vial	Solution for injection in vial
Vaccine/product formulation:	A/Hong Kong/125/2017-like (H7N9) (7.5 µg HA); Water for injections q.s. 0.25 mL	AS03B: DL-α-tocopherol and squalene in an o/w emulsion (5.93 mg DL-α-tocopherol); Water for injections q.s. 0.125 mL	A/Hong Kong/125/2017-like (H7N9) (7.5 µg HA); Water for injections q.s. 0.25 mL	AS03A: DL-α-tocopherol and squalene in an o/w emulsion (11.86 mg DL-α-tocopherol); Water for injections q.s. 0.25 mL	Sodium Chloride (3.85 mg); Potassium Chloride (100 µg); Magnesium Chloride (50 µg); Disodium Hydrogen Phosphate (1.3 mg); Potassium Dihydrogen Phosphate (186 µg); Water for injections q.s. 0.5 mL
Volume to be administered:	0.375 milliliter(s)		0.5 milliliter(s)		0.5 milliliter(s)
Number of doses to be administered:	2		2		2
Route of Administration:	Intramuscular use				
Administration site:					
Location	Deltoid				
Directionality	Not applicable				
Laterality****	Non-dominant				
Packaging and Labelling:	Refer to the Standard Procedures Manual for more details				
Manufacturer:	GSK Biologicals SA				
Type of contact/ Time points:	Visit 1 (Day 1), Visit 2 (Day 22)				

* 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).
*** Placebo: formulation buffer S9b is a phosphate buffered saline.
**** 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.
o/w: oil/water
q.s.: "Quantity sufficient" stands for the Latin term "quantum satis" which means "as much as necessary" i.e. adding enough of a constituent to achieve a specific final volume or total weight. QS is a placeholder for an amount or volume which has to be "adjusted" by the given circumstances in a particular preparation [EMA]

The participants must be observed closely for at least 30 minutes after the administration of the vaccine/product. Appropriate medical treatment must be readily available during the observation period in case of anaphylaxis and/or syncope.

6.2. Preparation/Handling/Storage/Accountability

The study vaccine/product must be stored in a safe, locked place at the temperature specified on the vaccine/product label. The storage temperature should be continuously monitored with calibrated (if not validated) temperature monitoring device(s) and recorded. Only authorized study personnel should be allowed access to the study vaccine/product. Storage conditions will be assessed by a sponsor study contact during pre-study activities. Refer to the section on Study Supplies in the SPM for more details on storage and handling of the study vaccine/product.

6.3. Measures to minimize bias: randomization and blinding

6.3.1. Participant identification

Participant identification numbers will be assigned sequentially to the participants who have consented to participate in the study, according to the range of participant identification numbers allocated to each study center.

6.3.2. Randomization to study intervention

The randomization list used to number the supplies will be based on a blocking scheme using a 1:1:1:1:1:1:1 ratio (approximately 120 participants in each study group).

The intervention numbers will be allocated by component.

To allow GSK to take advantage of greater rates of recruitment than anticipated at individual centers in this multi-center study and to reduce the overall study recruitment period, an over-randomization of supplies of at least 5% will be prepared.

6.3.3. Intervention allocation to the participant

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.

Central randomization will be performed using PPD Interactive Response Technology (IRT).

Allocation of the participant to a study group at the investigator site will be performed using the PPD IRT.

The IRT will determine the study group and will provide the intervention number to be used for the first vaccination. The intervention number(s) to be used for subsequent dose administration(s) will be provided by the same IRT.

The number of each administered intervention kit must be recorded in the eCRF on the Vaccine Administration form/screen.

Refer to the SPM for additional information relative to the intervention number allocation.

6.3.4. Allocation of participants to assay subsets

Vaccine-homologous microneutralization (MN) will be evaluated in a subset of approximately 420 participants (60 per group). A selection consistent of approximately 50% of participants per H7N9 vaccine group, and approximately 50% of participants from the placebo group will be generated.

PPD will select the first 30 participants per treatment group in the ≥ 65 age group and then the first 15 participants in 18 to 49 years and 50 to 64 years age groups. If there are not 15 participants for the 18 to 49 or 50 to 64 years age groups, PPD will select whichever has the smaller number fully and then have a total of 30 for the total among these 2 age groups per treatment group.

All samples will be collected first, then selected for the subset. PPD will supply the list of selected participants to Q^2 Solutions.

6.3.5. Blinding and unblinding

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, efficacy).

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 participant's intervention assignment is warranted. Please refer to the Section 6.3.5.1 for details regarding emergency unblinding.

A statistical team will be unblinded for the interim analysis outlined in Section 9.5.

6.3.5.1. Emergency unblinding

Unblinding a participant's individual intervention number should occur ONLY in case of a medical emergency when knowledge of the intervention is essential for the clinical management or welfare of the participant.

The emergency unblinding process enables the investigator to have unrestricted, immediate and direct access to the participant's individual study intervention via IRT.

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 participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact PPD prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant. If a participant's intervention assignment is unblinded, PPD must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable. Refer to Section 8.3.3.1 for emergency contact information.

6.3.5.2. Unblinding prior to regulatory reporting of SAEs

A participant may continue in the study if that participant's intervention assignment is unblinded provided that there are no safety concerns for the participant per the investigator's judgement.

GSK policy (which incorporates International Council on Harmonisation [ICH] E2A guidance, the EU Clinical Trial Directive and US Federal Regulations) is to unblind the report of any unexpected Serious Adverse Event (SAE) and which is attributable/suspected to be attributable to the study vaccine/product, prior to regulatory reporting. Vaccines Clinical Safety and Pharmacovigilance (VCSP) is responsible for unblinding the intervention assignment in accordance with the specified timeframes for expedited reporting of SAEs (refer to the Section 10.3.10.1).

In addition, GSK VCSP staff may unblind the intervention assignment for any participant with a Suspected Unexpected Serious Adverse Reaction (SUSAR) or an SAE that is fatal or life threatening. If the SAE requires an expedited regulatory report be sent to 1 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

All doses will be administered at the site under medical supervision. Each dose will be administered by an unblinded member of the site staff who could also participate in dose preparation but who is barred from participation in any other study functions and cannot contribute to any observations. The date and time of each dose administered in the clinic will be recorded in the source documents and in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. The number of each administered intervention kit must be recorded in the eCRF on the Vaccine Administration form/screen.

6.5. Concomitant therapy

At each study visit, the investigator or delegate should question the participant about any medications/products taken and vaccinations received by the participant.

The following concomitant medications/products/vaccines must be recorded in the eCRF:

- All concomitant vaccines/medications/products associated with an AE, except vitamins and dietary supplements, administered following the first dose of study vaccine (Day 1 to Day 43).
- Any concomitant medications/products/vaccines leading to the withdrawal or non-eligibility of the participant from the study.
- Any concomitant medications/products/vaccines relevant to an SAE/potential immune-mediated disease (pIMD) to be reported as per protocol or administered at any time during the study period for the treatment of an SAE/pIMD. Concomitant medications relevant to SAEs and pIMD must be recorded on the Expedited Adverse Events report.

An antipyretic is considered prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring.

The PPD Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.6. Dose modification

Not applicable

6.7. Intervention after the end of the study

No intervention is planned after participants complete the study. No additional care will be provided to participants after they complete or discontinue the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of study intervention

'Discontinuation' of study vaccine/product means any participant who has not received all planned doses of vaccine/product. A participant who discontinued study vaccine/product should be encouraged to, if deemed appropriate by the investigator, continue other study procedures (e.g. safety or immunogenicity) if planned in the study protocol.

The primary reason for premature discontinuation of the study vaccine/product will be documented on the eCRF based on the following:

- Adverse event requiring expedited reporting to GSK
- Unsolicited non-SAE
- Solicited AE
- Protocol deviation
- Not willing to be vaccinated
- Other (specify).

7.1.1. Criteria for temporary delay for enrollment and/or vaccination

Vaccination may be postponed within the permitted time interval until transient circumstances cited below are resolved:

- Acute disease and/or fever at the time of vaccination. Refer to the SoA (Section 1.3) for fever definition and preferred location for measuring temperature in this study.
- 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.
- Use of antipyretics and/or analgesics and/or antibiotics within 12 hours prior to vaccination.

7.1.2. Contraindications to subsequent vaccine(s) administration

Participants must be evaluated to confirm they are eligible for subsequent vaccination before administering each additional study vaccine 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 vaccinations. However, these participants should be encouraged to continue other study procedures at the discretion of the investigator (Section 10.3.8.2). The relevant criteria for discontinuing vaccination must be recorded in the eCRF.

- Participants who experience any SAE judged to be possibly or probably related to study vaccine or non-study vaccines, including hypersensitivity reactions.
- Participants who develop any new condition which, in the opinion of the investigator, may pose additional risk to the participant if he/she continues to participate in the study.
- Anaphylaxis following the administration of vaccine/product.
- 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, expose the participant to unacceptable risk from subsequent vaccination. In such cases, the investigator should use his/her clinical judgment prior to administering the next dose of the vaccine/product. Refer to Section 10.3.5.1 for the definition of pIMDs.

7.2. Participant discontinuation/withdrawal from the study

A participant is considered a 'withdrawal' from the study when no study procedure has occurred, no follow-up has been performed and no further information has been collected for this participant from the date of withdrawal/last contact.

From an analysis perspective, a 'withdrawal' from the study refers to any participant who was not available for the concluding contact foreseen in the protocol.

Investigators will attempt to contact those participants who do not return for scheduled visits or follow-up.

All data and samples collected until the date of withdrawal/last contact of the participant will be used for the analysis.

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

- Adverse events requiring expedited reporting to GSK
- Unsolicited non-SAE
- Solicited AE
- Protocol deviation
- Withdrawal by participant, not due to an AE*
- Migrated/Moved from the study area
- Lost to follow-up
- Sponsor study termination
- 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 10.3.8.2).

7.3. Lost to follow-up

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

Please refer to the SPM for a description of the actions to be taken before considering the participant as lost to follow-up.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3).

Adherence to the protocol is required for study conduct.

Protocol waivers or exemptions are not allowed unless necessary for the management of an immediate safety concerns.

The investigator is not allowed to do testing on samples outside of what has been agreed upon by the Independent Ethics Committee (IEC)/Institutional Review Board (IRB).

Immediate safety concerns should be discussed with the sponsor as soon as they occur or when the study team is aware of them. The purpose of this communication is to determine if the participant(s) should discontinue the study intervention.

All screening evaluations must be completed and the results reviewed before confirming that potential participants meet all eligibility criteria.

The investigator will maintain a screening log of all participants screened. All relevant information, such as confirmation of eligibility and reasons for screening failure will be mentioned in this screening log.

Procedures conducted as part of routine clinical management (e.g. hematologic profiles) and obtained before the participant signed the Informed Consent Form (ICF) may be used for screening and/or for establishing a clinical baseline, provided the procedure met protocol-specified criteria and was performed within the time frame defined in the SoA (Section 1.3).

The SPM provides the investigator and site personnel with administrative and detailed technical information that does not impact participant safety.

8.1. Efficacy and/or immunogenicity assessments

Collected biological samples will be used for protocol mandated research and purposes related to the improvement, development and quality assurance of the laboratory tests described in this protocol.

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 GSK or a contracted partner to use the samples for future research. Future research will be subject to prior IEC/IRB approval if required per local legislation.

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

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 8.1.3 may be changed.

Collected samples will be stored for a maximum of 20 years. 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 to, and discussed and agreed with, GSK.

8.1.1. Biological samples

Approximately 80 mL of blood will be collected during the entire study period.

Table 7 Biological samples

Sample type	Quantity	Unit	Time point	Subset name*
Blood	At least 25 mL	mL	Days 1, 22, and 43	All participants

* Refer to Section 6.3.4 for subset description.

8.1.2. Laboratory assays

All laboratory testing will be performed in a laboratory designated by GSK Biologicals.

Microneutralization and hemagglutination inhibition (HI) assays development, qualification and clinical testing will be outsourced.

Table 8 Laboratory assays

Assay type	System	Component	Challenge	Method	Laboratory*
Humoral Immunity (Antibody determination)	Serum	Vaccine-homologous Influenza A/Hong Kong/125/2017-like Virus		HI	Q² Solutions
	Serum	Vaccine-homologous Influenza A/Hong Kong/125/2017-like Virus		MN	Q² Solutions

* Refer to the list of clinical laboratories for details.
HI: hemagglutination inhibition; MN: microneutralization

Please refer to the 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.

The clinical laboratories have established a Quality System supported by procedures. The activities of the clinical laboratories are audited regularly for quality assessment by an internal (sponsor-dependent) but laboratory-independent Quality Department. Clinical laboratories contracted by GSK also conform to Good Laboratory Practice guidelines and operate in compliance with regulatory standards.

8.1.3. Immunological read-outs

Table 9 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	840	Vaccine-homologous Influenza A/Hong Kong/125/2017-like Virus	1
Visit 1 (Day 1)	Pre-Vacc I	MN	420	Vaccine-homologous Influenza A/Hong Kong/125/2017-like Virus	2
Visit 2 (Day 22)	Pre-Vacc II	HI	840	Vaccine-homologous Influenza A/Hong Kong/125/2017-like Virus	1
Visit 2 (Day 22)	Pre-Vacc II	MN	420	Vaccine-homologous Influenza A/Hong Kong/125/2017-like Virus	2
Visit 3 (Day 43)	Post-Vacc II	HI	840	Vaccine-homologous Influenza A/Hong Kong/125/2017-like Virus	1
Visit 3 (Day 43)	Post-Vacc II	MN	420	Vaccine-homologous Influenza A/Hong Kong/125/2017-like Virus	2

HI: hemagglutination inhibition; MN: microneutralization; Post-Vacc: post-vaccination; Pre-Vacc: pre-vaccination

8.1.4. 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 [Rimmelzwaan, 2008]

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 antibody titers of 1:40 or greater have been associated with protection from influenza illness in at least 50% of participants in challenge studies [Hannoun, 2004] and correlate with vaccine effectiveness [Beyer, 1989].

8.2. Safety Assessments

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE. 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.

8.2.1. Pre-vaccination procedures

8.2.1.1. Informed consent

The signed informed consent of the participant must be obtained before study participation. Refer to Section 10.1.3 for the requirement on how informed consent will be obtained.

8.2.1.2. Check inclusion and exclusion criteria

All inclusion and exclusion criteria will be checked as described in Sections 5.1 and 5.2 before dosing on Day 1.

8.2.1.3. Collection of demographic data

Demographic data such as age, year of birth, gender, height, weight, race, and ethnicity will be recorded in the participant's eCRF.

8.2.1.4. Medical history

Obtain the participant's medical history by interviewing the participant and/or review of the participant's medical records. Record any pre-existing participant conditions, signs and/or symptoms present prior to the first vaccination in the eCRF.

8.2.1.5. Physical examination

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 heart rate and 1 blood pressure measurement. Blood pressure and pulse measurements will be assessed by a completely automated device. Manual techniques will be used only if an automated device is not available. Collected information will be recorded in the eCRF.

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

8.2.1.6. History of adjuvanted vaccine and influenza vaccine

For each of the 2017/2018, 2018/2019, and 2019/2020 influenza seasons, record whether the participant received an adjuvanted vaccine or influenza vaccine and if so, the administration method in the eCRF.

8.2.1.7. Pregnancy test

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 vaccine/product may only be administered if the pregnancy test is negative.

Refer to the Section 10.5.3.1 for the information on study continuation for participant who becomes pregnant during the study.

8.2.1.8. Assess pre-vaccination body temperature

The body temperature of the participant must be measured prior to any study vaccine/product administration. The preferred location for recording temperature in this study is oral. If the participant has a temperature ≥ 38.0°C/100.4°F by any route on the day of dosing, the dosing visit will be rescheduled within the allowed interval (Table 2).

8.2.2. Study holding rules and safety monitoring

8.2.2.1. Internal Safety Review Committee

At least 2 iSRC reviews are planned.

The iSRC members are GSK employees and will not be otherwise involved in the conduct of the study and will be independent from GSK's Pandemic Influenza Safety Review Team. The iSRC members will have access to all available data. The iSRC composition, responsibilities and operational details will be outlined in an iSRC charter.

8.2.2.2. Outcome of safety evaluation

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.

8.2.2.3. Study holding rules

The safety holding rules are defined in Table 10. 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.

The final responsibility to recommend whether the study should be continued in all or in selected groups, modified or stopped permanently, rests with the Sponsor, after having considered all the safety information available. If the study is stopped or modified, a letter indicating the reasons will be sent to the IRB(s)/IEC(s) via the investigator(s), and to Center for Biologics Evaluation and Research (CBER), via GSK.

Of note, no formal holding rules will be applied for other safety data such as non-life-threatening SAEs, missed visits due to vaccine-related AEs, Grade 1 and Grade 2 solicited administration site and systemic events and unsolicited AEs in the 7-day follow-up period and unsolicited AEs collected from Day 8 to Day 22 and Day 29 to Day 43 after vaccination. However, if available, these data will also be reviewed by the iSRC in order to allow an overall assessment of the benefit/risk ratio of vaccination.

Table 10 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

If any investigator becomes aware of a holding rule being met, he/she will suspend vaccination and inform the PPD Medical Monitor immediately (e.g. meeting of holding rules 1a-b). Refer to the Table 13 for contact information.

When a holding rule is identified the following communication flow will occur:

1. The investigator will notify the PPD Medical Monitor by calling the PPD Pharmacovigilance SAE Hotline at 1-800-201-8725.
2. The PPD Medical Monitor or delegate will notify the study sites and IRT manager. The IRT manager will block IRT from allowing randomization (or screening, if applicable). Study sites will not randomize or screen participants until notification that the hold is released.
3. The study site will confirm receipt of notification (in writing). Clinical team manager at PPD will collect study site acknowledgement.
4. PPD Medical Monitor will notify GSK Clinical Research and Development Lead.

5. GSK Clinical Research and Development Lead will notify Vaccine Safety Monitoring Board (VSMB) and iSRC.
6. iSRC will review unblinded data and make recommendation to VSMB.
7. VSMB will make final decision whether to continue or stop the study.
8. GSK will notify CBER.

8.3. Adverse Events (AEs), Serious Adverse Events (SAEs) and other events of interest

8.3.1. Time period and frequency for collecting AE, SAE and other safety information

Table 11 Timeframes for collecting and reporting of safety information

Event	Pre-V1*	V1 D1	D7	V2 D22	D28	V3 D43	TC3 M4	TC4 M7	TC5 M10	TC6 M13
Solicited administration site and systemic events										
Unsolicited AEs and MAEs										
SAEs										
Pregnancy										
pIMDs										

* i.e. consent obtained.
AEs: adverse events; D: Day; M: Month; MAEs: medically attended adverse events; pIMDs: potential immune-mediated diseases; Pre-V: pre-vaccination; SAE: serious adverse events; TC: telephone contact; V: vaccination

The investigator or designee will record and immediately report all SAEs to the sponsor or designee via the Expedited AE Reporting Form. This reporting should, under no circumstances, occur later than 24 hours after the investigator becomes aware of an SAE, as indicated in Section 10.3.10. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting periods defined in Table 11. Investigators are not obligated to actively seek AEs or SAEs in former study participants. 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 to be reasonably related to the study vaccine/product, the investigator will promptly notify the Study Contact for Reporting SAEs mentioned in the Table 13.

8.3.2. Method of detecting AEs and SAEs, pregnancies and other events

Methods of detecting and recording AE/SAE/pIMDs/pregnancies are detailed in the Section 10.3.8. The assessment of AE/SAE intensity, causality and outcome are provided in the Section 10.3.9.

Open-ended and non-leading verbal questioning of the participants is the preferred method of acquiring information related to an AE/SAE/pIMDs/pregnancy.

8.3.2.1. Clinically significant abnormal laboratory findings

Clinical laboratory measurements are not scheduled to be taken during the study; however, clinical laboratory tests may be performed and the results obtained as part of critical care or follow-up due to the occurrence of medically attended adverse events (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.

8.3.3. Regulatory reporting requirements for SAEs, pregnancies, and other events

Once an investigator (or designee) becomes aware that a study participant has experienced an SAE/pIMDs/pregnancy, he/she must report it to PPD Pharmacovigilance using the required documentation, and within the timeframes, mentioned in the Table 12. This is essential for meeting legal obligations and ethical responsibilities for participant safety and the safety of a study intervention under clinical investigation.

For SAEs/pIMDs, the investigator will always provide an assessment of causality at the time of the initial report, as defined in the Section 10.3.9.2.

Local regulatory requirements and sponsor policy for the preparation of an investigator safety report for SUSAR must be followed. These reports will be forwarded to investigators as necessary.

The sponsor has a legal responsibility to notify regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements related to safety reporting to the regulatory authority, IRB/IEC, and investigators.

Please refer to Section 10.3.10 for further details regarding the reporting of SAEs/pIMDs/pregnancies.

Table 12 Timeframes for submitting serious adverse event, pregnancy and other events reports to PPD Pharmacovigilance

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours* ‡	Electronic Expedited Adverse Events Report	24 hours*	Electronic Expedited Adverse Events Report
Pregnancies	***24 hours**** **(Amended 22 February 2022)**	Paper pregnancy notification report	***24 hours**** **(Amended 22 February 2022)**	Paper pregnancy follow-up report
pIMDs	24 hours** ‡	Electronic Expedited Adverse Events Report	24 hours*	Electronic Expedited Adverse Events Report

* 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 pIMDs.
‡ The investigator will be required to confirm review of the SAE/pIMDs causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE/pIMDs.

8.3.3.1. Contact information for reporting of SAEs, pIMDs, pregnancies and study holding rules

Table 13 Contact information for reporting of SAEs, pIMDs, pregnancies and study holding rules

Study contact for questions regarding SAEs, pIMDs, pregnancies Refer to the local study contact information document	**Study contact for reporting of study holding rules** As soon as the investigator is aware that a holding rule is met, he/she must immediately inform the PPD Medical Monitor (refer to Section 8.2.2.3).
Back-up study contact for reporting SAEs, pIMDs, pregnancies Available 24/24 hours and 7/7 days: **PPD Clinical Safety & Pharmacovigilance** SAE Hotline for North America Phone: 1-800-201-8725 Fax: 1-888-488-9697 E-mail: WIL Safety (SM) wilsafety@ppdi.com	**Back-up study contact for escalation of holding rules** PPD Pharmacovigilance Phone: 1-800-201-8725 Fax: 1-888-488-9697

8.3.4. 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 (refer to the Section 10.3.10.1).

8.3.5. Participant card

The investigator (or designee) must provide the participant with a "participant card" containing information about the clinical study. The participant must be instructed to keep the participant card in his/her/their possession at all times throughout the study. In an emergency, this card serves to inform the responsible attending physician that the participant is in a clinical study and that relevant information may be obtained by contacting the investigator.

8.4. Treatment of overdose

For this study, any dose of study intervention greater than 1.9 µg, 3.75 µg, or 7.5 µg given outside of the Study Day 18 to Study Day 25 interval will be considered an overdose.

GSK does not recommend specific treatment for an overdose.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Not applicable

8.8. Biomarkers

Not applicable

8.9. Health outcomes

Not applicable

9. STATISTICAL CONSIDERATIONS

9.1. Statistical hypotheses

The hypothesis test is planned to demonstrate whether vaccination with monovalent influenza A/Hong Kong/125/2017-like (H7N9) virus vaccine containing 1.9 µg, 3.75 µg or 7.5 µg of HA adjuvanted with AS03A or AS03B elicits an HI antibody response to the vaccine-homologous virus that meets or exceeds the CBER immunogenicity criteria 21 days after the second dose of H7N9 vaccine [CBER, 2007].

Each null hypothesis (H_0) is that the lower limit (LL) of the confidence interval (CI) for seroconversion (SCR)/seroprotection (SPR) rate will not meet or exceed the threshold set in the CBER guidelines. Each alternative hypothesis (H_a) is that the LL of the CI for the SCR/SPR meets or exceeds the threshold set in the CBER guidelines. The overall type I error rate is fixed at 5% for each age group, and a Bonferroni adjustment was applied to allow simultaneous multiple comparisons of each antigen/adjuvant group.

9.2. Sample size determination

Approximately 840 participants will be randomized to achieve 798 evaluable participants.

Withdrawals will not be replaced.

9.2.1. Immunogenicity

The primary immunogenicity objective of the study is to evaluate whether vaccination with monovalent influenza A/Hong Kong/125/2017-like (H7N9) virus vaccine containing 1.9 µg, 3.75 µg or 7.5 µg of HA adjuvanted with AS03A or AS03B elicits an HI antibody response to the vaccine-homologous virus that meets or exceeds the US Food and Drug Administration, CBER immunogenicity criteria at the Day 43 visit. [CBER, 2007].*

* 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 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 SCR 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%.

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 treatment 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 within each age group, addressing multiple comparisons using a Bonferroni adjustment by dividing the 5% Type I error equally 6 ways. Success can be declared for any antigen/adjuvant group within an age range if CBER criteria is met even if any other group does not meet the CBER criteria.

Table 14 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 14 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	Statistical Success Criteria	N evaluable	Reference value	Power*
18-64 years of age	Anti-HA: SCR	LL of 99.17% CI of SCR > 40%	57	80%	99.99%*
	Anti-HA: SPR	LL of 99.17% CI of SPR > 70%	57	91%	86.26%*
≥65 years of age	Anti-HA: SCR	LL of 99.17% CI of SCR > 30%	57	75%	>99.99%*
	Anti-HA: SPR	LL of 99.17% 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%.
CBER: Center for Biologics Evaluation and Research; CI: confidence interval; HA: hemagglutinin; LL: lower limit; SCR: seroconversion rate; SPR: seroprotection rate.

9.2.2. Safety

In this study, descriptive safety assessment of the different vaccine formulations is a primary objective. Table 15 presents the 95% CIs for a given percentage of participants reporting a symptom after vaccination, assuming a sample size of 60 participants per vaccine group.

Table 15 Exact 95% CI on the percentage of participants with AEs following vaccination for 60 participants per group

Number of participants with a symptom	% of participants with a symptom (N=60)	95% confidence interval	
		Lower Limit	Upper Limit
0	0	0	6
1	1.7	0	8.9
2	3.3	0.4	11.5
3	5	1	13.9
4	6.7	1.8	16.2
5	8.3	2.8	18.4
6	10	3.8	20.5
7	11.7	4.8	22.6
8	13.3	5.9	24.6
9	15	7.1	26.6
10	16.7	8.3	28.5
11	18.3	9.5	30.4
12	20	10.8	32.3
13	21.7	12.1	34.2
14	23.3	13.4	36
15	25	14.7	37.9
16	26.7	16.1	39.7
17	28.3	17.5	41.4
18	30	18.8	43.2
19	31.7	20.3	45
20	33.3	21.7	46.7
21	35	23.1	48.4
22	36.7	24.6	50.1
23	38.3	26.1	51.8
24	40	27.6	53.5
25	41.7	29.1	55.1
26	43.3	30.6	56.8
27	45	32.1	58.4
28	46.7	33.7	60
29	48.3	35.2	61.6
30	50	36.8	63.2

9.3. Populations for analyses

Table 16 Populations for analyses

Analysis set	Description
Enrolled	Participant's agreed to participate in a clinical study after completion of the informed consent process. Refer to the Glossary of terms for the definition of 'enrolled'.
Randomized	All participants who were randomized to receive a study vaccine.
Exposed *Set* (ES) (Amended 22 February 2022)	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.
Full Analysis Set (FAS) 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).
FAS 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).
Per Protocol Set (PPS) 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). Major protocol deviations leading to exclusion will be defined in the Statistical Analysis Plan (SAP) and the Study Deviation Rules document and will be finalized prior to the interim analysis defined in Section 9.5. Primary immunogenicity data will be evaluated based on this set.
Modified PPS (mPPS) 1	***The mPPS 1 is a subset of FAS 1. The mPPS 1 includes all FAS 1 participants with no major protocol deviations that led 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 between 18-32 study days. The interval between Visit 2 and Visit 3 will be 14-32 calendar days.*** ***Major protocol deviations leading to exclusion will be defined in the Statistical Analysis Plan (SAP) and the Study Deviation Rules Document and will be finalized prior to the interim analysis defined in Section 9.5.*** **(Amended 22 February 2022)**
PPS 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). Major protocol deviations leading to exclusion will be defined in the SAP and the Study Deviation Rules document and will be finalized prior to the interim analysis defined in Section 9.5. Secondary immunogenicity data will be evaluated based on this set.
mPPS 2	***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 between 18-32 study days.*** ***Major protocol deviations leading to exclusion will be defined in the SAP and the Study Deviation Rules document and will be finalized prior to the interim analysis defined in Section 9.5.*** **(Amended 22 February 2022)**
Microneutralization (MN)	All participants in the Randomized Set who were also selected to the subset of MN evaluation.
Microneutralization Per Protocol Set (MNPPS) 1	All participants in the MN Set who are also part of the PPS 1.
MN mPPS 1	***All participants in the MN Set who are also part of the mPPS 1.*** **(Amended 22 February 2022)**
MNPPS 2	All participants in the MN Set who are also part of the PPS 2.
MN mPPS 2	***All participants in the MN Set who are also part of the mPPS 2.*** **(Amended 22 February 2022)**

9.3.1. Criteria for elimination from analysis

9.3.1.1. Intercurrent medical conditions and concomitant medications/products/vaccines that may lead to elimination of a participant from per-protocol analyses

If the participant meets one of the criteria mentioned in the Section 7.1.2, he/she may be eliminated from per protocol analysis sets.

If the participant has a protocol deviation deemed as major, he/she may be eliminated from the per protocol analysis sets. Major protocol deviations leading to exclusion will be defined in the Statistical Analysis Plan (SAP) and the Study Deviation Rules document and 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 entry criteria including age at enrollment
- Participants incorrectly vaccinated
- Participants who did not receive study vaccinations as planned in protocol
- 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

These key major deviations will be assessed based on the data collected in the eCRFs.

9.4. Statistical analyses

9.4.1. General considerations

Derived and transformed data:

- Immunogenicity (Note: The cut-off value for antibody titer is defined by the laboratory before the analysis and will be specified in the clinical study report).
  - A seronegative participant is a participant whose antibody titer is below the assay cut-off value.
  - A seropositive participant is a participant whose antibody titer is greater than or equal to the assay cut-off value.
  - Seroprotection is defined as an HI antibody titer ≥ 40 1/DIL.
  - SPR is defined as the percentage of participants with an HI antibody titer ≥ 40 1/DIL.
  - Seroconversion 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.
- Vaccine response 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) is defined as the percentage of participants with vaccine response.
- The geometric mean titers (GMTs) calculations are performed by taking the anti-log of the mean of the log concentration/titer transformations. Values for the antibody concentrations/titers below the assay cut-off will be assigned half the assay cut-off value 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 ***applicable*** Per Protocol Set (PPS) ***as described in Section 9.3 (Table 16)***. ***Supplementary analyses for primary and secondary HI immunogenicity analyses will be based on the applicable mPPS.*** If the difference between PPS ***1*** and FAS ***1*** is greater than 10%, a second analysis based on the FAS will be performed to complement the PPS analysis. **(Amended 22 February 2022)**
- The MN immunogenicity analyses will be based on the ***applicable*** Microneutralization Per Protocol Set (MNPPS) ***as described in Section 9.3 (Table 16)***. ***Supplementary analyses for MN immunogenicity analyses will be based on the applicable MN mPPS.*** **(Amended 22 February 2022)**

- 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 Exposed Set (ES) 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.
- 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. No randomization stratification or enrollment constraints will be imposed for these additional age categorizations.

9.4.2. Participants disposition

Participant disposition will be summarized for the ES, for each study group, age 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 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.

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

Major deviations will be summarized for the ES for each study group, age group, and overall. The reason for elimination from the PPS 1 and PPS 2 ***and mPPS 1 and mPPS 2*** will also be summarized. ***The same will be done for MNPPS 1, MNPPS 2, MN mPPS 1 and MN mPPS 2.*** **(Amended 22 February 2022)**

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

9.4.3. Primary endpoint(s)

9.4.3.1. Immunogenicity

Primary immunogenicity analyses will be based on the PPS 1 set.

Supplementary immunogenicity analyses will be based on the mPPS 1 set. **(Amended 22 February 2022)**

The following aggregate variables will be calculated for each vaccine group for vaccine homologous H7N9 HI antibody titer along with Clopper-Pearson exact two-sided 99.17% CIs:

- SCR at Day 43
- SPR at Day 43

9.4.3.2. Safety

The analysis of reactogenicity and unsolicited events will be based on the ES.

Solicited administration site and systemic endpoints

- Occurrence of each solicited administration site events during a 7-day follow-up period (Day 1 to Day 7) after each vaccination.
- Occurrence of each solicited systemic events during a 7-day follow-up period (Day 1 to Day 7) after each vaccination.

All solicited events will be summarized according to defined severity grading scales.

Frequencies and percentages of participants experiencing each event will be presented for each symptom severity. Summary tables showing the occurrence of any solicited administration site events or solicited systemic events overall and at each time point will

also be presented and will be tabulated with Clopper-Pearson exact 95% CIs. Solicited administration site events will be assessed according to which vaccine was administered.

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. Summary tables showing the occurrence of any solicited administration site events or solicited systemic events overall will be presented.

Unsolicited AE endpoints (Amended 22 February 2022)

- Occurrence and relationship to vaccination of unsolicited AEs within 21 days after each vaccination.
- Occurrence and relationship to vaccination of AEs with MAEs within 21 days after each vaccination.

SAE endpoints

- Occurrence and relationship to vaccination of SAEs and pIMDs up to Day 43 visit.
- Occurrence and relationship to vaccination of SAEs and pIMDs until Month 13.

This analysis applies to all AEs, whether judged either as probably related, possibly related, or not related to vaccination by the investigator, recorded in the Adverse Events eCRF, with a start date on or after the date of first vaccination and not later than 21 days of the most recent vaccination. Adverse events starting prior to the first vaccination will only be listed. The original verbatim terms used by investigators to identify AEs in the eCRFs will be mapped to preferred terms using the Medical Dictionary for Regulatory Activities. The AEs will then be grouped by Medical Dictionary for Regulatory Activities preferred terms into frequency tables according to system organ class.

All reported AEs, as well as AEs judged by the investigator as at least possibly related to study vaccine(s), will be summarized according to system organ class and preferred term within system organ class. These summaries will be presented by study group and by interval of study observation. When an AE occurs more than once for a participant, the maximal severity and strongest relationship to the study group will be counted.

Separate summaries will be produced for the following categories:

- SAEs
- AEs that are possibly or probably related to vaccine(s)
- AEs leading to withdrawal
- MAEs
- pIMDs

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)

9.4.4.1. Immunogenicity

The following aggregate variables will be calculated for each vaccine group for vaccine homologous H7N9 HI antibody titer:

- 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

For a subset of participants (MNPPS 1 and MNPPS 2 sets ***and MN mPPS 1 and MN mPPS 2***), the following aggregate variables will be calculated for each vaccine group for vaccine-homologous H7N9 MN antibody titer: **(Amended 22 February 2022)**

- GMTs at Days 1, 22, and 43
- Seropositivity rates at Days 1, 22, and 43
- VRR at Days 22 and 43

The GMTs/MGIs with 95% CIs will be tabulated by visit for each treatment group, age group and overall. For seropositivity/VRR, percentage of participants will be calculated with Clopper-Pearson exact two-sided 95% CIs. For SCR/SPR, percentage of participants will be calculated with Clopper-Pearson exact two-sided 99.17% CIs.

9.4.5. Other analyses

9.4.5.1. Demography and baseline characteristics analyses

Demographic characteristics (age, gender, race, center, height, weight, and ethnicity) will be tabulated per study group for each analysis set, age group and overall as described in the SAP.

The mean of continuous variables (plus range and standard deviation) of the enrolled participants, as a whole and per study group, age group and overall, will be calculated.

The distribution of discrete variables will be tabulated as a whole and per study group, age group and overall as described in the SAP.

The analysis of demographics will be performed separately for the ES and for the participants contributing to the PPS ***(and mPPS)***. (**Amended 22 February 2022)**

Demographic characteristics (including but not limited to age, gender, race, height, weight, and ethnicity) will be summarized by group using descriptive statistics:

- For categorical variables such as center, the number and frequency in each category will be provided.
- Number (number of participants in the analysis), mean, median, minimum and maximum, and standard deviation will be provided for continuous data such as age.

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

9.4.5.2. COVID-19 assessments

Frequencies and percentages of participants with suspected, probable, or confirmed COVID-19 cases will be summarized for the ES for each study group, age group, and overall. Additional COVID-19 case details will be presented in data listings.

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 (eg, 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 9.3.1.

If study procedures are modified due to special circumstances, there may be requirement to conduct analyses that separately describe the data collected during the period of modified study procedures.

9.5. Interim analyses

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, BARDA, and regulatory agency review, 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. 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 collected 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 after each vaccination on as clean as possible data.*** **(Amended 22 February 2022)**
- Analyses of SAEs, pIMDs, pregnancies and withdrawals due to AEs collected up to the Day 43 post-vaccination visit will be carried out. **(Amended 22 February 2022).**
- 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 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.

9.5.1.2. Final analysis (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 21 days after each vaccination. **(Amended 22 February 2022)**
- Concomitant medications reported up to ***21 days after each vaccination***. **(Amended 22 February 2022)**
- SAEs, pIMDs, 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 ***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. **(Amended 22 February 2022)** For the primary immunogenicity analysis, which will be reported at Day 43 the overall type I error rate is fixed at 5% and

a Bonferroni adjustment will be applied to allow simultaneous multiple comparisons of each antigen/adjuvant group. For the primary safety analyses no adjustment for multiple comparisons will be made in each antigen/adjuvant group.

9.6. Data Monitoring Committee (DMC)

Not applicable

10. 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:
  - 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 or Informed Assent Form, IB, and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC by the investigator for review and approval. These documents will be signed and dated by the investigator before the study is initiated.
- Any protocol amendments will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.
- 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 SAE(s) or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2. 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 financial interest information prior initiation of the center and at the end of the study. Investigators are responsible for providing a Financial Disclosure update if their financial interests change at any point during their participation in a study and for 1 year after completion of the study.

10.1.3. Informed consent process

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary.

Freely given and written informed consent must be obtained from each participant, as appropriate, prior to participation in the study.

The content of the ICF must meet the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.

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

Participants must be re-consented to the most current version of the ICF(s) or an ICF addendum during their participation in the study.

A copy of the ICF(s) must be provided to the participants.

10.1.4. 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 participants must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law.

The participants must be informed of their rights regarding the use of their personal data in accordance with the data privacy Section of the ICF.

The participants 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.

GSK will also ensure protection of the personal data of the investigator and site staff which will be collected within the framework and for the purpose of the study in accordance with the Data Privacy Notice that will be sent to the site staff.

10.1.5. Committees structure

Conduct of the study includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of study protocol and any subsequent amendments
- Participant informed consent
- Investigator reporting requirements as stated in the protocol.

Details for the structure of the iSRC can be found in Sections 8.2.2.1 and 8.2.2.2.

The details of the analyses to be provided to the iSRC will be fully described in the SAP.

10.1.6. 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 the 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 trial 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. The investigator is encouraged to share the summary results with the study participants, as appropriate.

GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

GSK intends to make anonymized patient-level data from this trial 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 trial participants are used to maximum effect in the creation of knowledge and understanding.

10.1.7. Data quality assurance

The investigator should maintain a record of the location(s) of their respective essential documents including source documents. The storage system used during the trial and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval.

Essential trial documents may be added or removed where justified (in advance of trial initiation) based on their importance and relevance to the trial. When a copy is used to replace an original document (e.g. source documents, CRF), the copy should fulfil the requirements for certified copies.

All participant data relating to the study will be recorded on printed or electronic CRF 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 electronically signing the eCRF.

The investigator must maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial participants (see Glossary of terms for the exact definition of source documents) that support information entered in the eCRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents or certified copies.

The sponsor or designee is responsible for the data management of this study including quality checking of the source data.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are 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). The safety and rights of participants must be protected and study be conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Trial records and source documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 15 years from the issue of the final Clinical Study Report/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.

10.1.8. Source documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Investigator should maintain a record of the location(s) of their source documents.

Data 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 source documents can be found in the Glossary of terms.

10.1.9. Study and site start and closure

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

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK, provided there is sufficient notice given to account for patient's safe exit from study participation. Study sites regular closure will occur upon study completion. A study site is considered closed when all required data/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:

- 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 recruitment of participants by the investigator
- Discontinuation of further study intervention development

At the end of the study, each investigator will:

- Review data collected to ensure accuracy and completeness
- Complete the Study Conclusion screen in the eCRF.

10.1.10. Publication policy

GSK aims to submit for publication the results of the study in searchable, peer reviewed scientific literature within 18 months from Last Subject Last Visit (LSLV) for interventional studies and follows the guidance from the International Committee of Medical Journal Editors.

10.2. Appendix 2: Clinical laboratory tests

Hemagglutination-inhibition Assay

Hemagglutination inhibition antibody 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 H7N9 influenza A specific antibody responses, such as those following influenza virus vaccinations. Briefly, serum samples are treated with receptor destroying enzyme overnight, diluted to 1:10, and serial diluted 2-fold in triplicate from 1:10 to 1:10240. After addition of an equal volume of standardized virus (4 HAU / 25 µL), neutralization is performed for 1 hour at room temperature, followed by addition of the red blood cells. After 30 minutes, 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 sera sample will be tested in triplicate within the same assay. The three titer results will be reported, as will the GMT for the triplicate.

Microneutralization Assay

Measurements are conducted on thawed frozen serum samples. Samples are heat inactivated for 30 minutes at 56°C. A standardized amount of virus is mixed with serial dilutions of serum and incubated 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 for 18 to 20 hours. 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 antibody titer is determined using a formula that calculates the midpoint optical density of uninfected cells and virus infected (without neutralization) cells.

10.2.1. Protocol-required safety laboratory assessments

There are no protocol-required safety laboratory assessments for this study.

10.3. Appendix 3: Adverse Events: definitions and procedures for recording, evaluating, follow-up, and reporting Definition of AE

10.3.1. Definition of an Adverse Event (AE)

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of 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 study intervention.

10.3.1.1. Events Meeting the AE Definition

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study vaccine/product administration even though they may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study vaccine/product or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs or symptoms temporally associated with study vaccine/product administration.
- Signs, symptoms that require medical attention (e.g. hospital stays, physician visits and emergency room visits)
- Pre- or post- intervention events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of participant's previous therapeutic regimen).
- Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will also be reported as AEs or SAEs.
- AEs to be recorded as solicited AEs are described in the Section 10.3.3. All other AEs will be recorded as UNSOLICITED AEs.

10.3.1.2. Events NOT Meeting the AE Definition

- Situations where an untoward medical occurrence did not occur (e.g. 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 conditions or signs and/or symptoms present in a participant prior to the first vaccination. These events will be recorded in the medical history section of the eCRF.
- Hospitalization for elective treatment of a pre-existing condition (known or diagnosed prior to informed consent signature) that did not worsen from baseline.
- Clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the participant's condition, or that are present or detected at the start of the study and do not worsen.

10.3.2. Definition of a Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that:	
a.	Results in death
b.	Is life-threatening Note: 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, had it been more severe.
c.	Requires hospitalization or prolongation of existing hospitalization Note: In general, hospitalization signifies that the participant has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or in an out-patient setting. Complications that occur during hospitalization are also considered as AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalization' occurred, or was necessary, the AE should be considered serious.
d.	Results in disability/incapacity Note: 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 like illness, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
e.	Is a congenital anomaly/birth defect in the offspring of a study participant
f.	Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy).
g.	Other situations Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be

immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.

10.3.3. Solicited events

a. Solicited administration site events

The following administration site events will be solicited:

Table 17 Solicited administration site events

All age groups
Pain
Redness
Swelling

b. Solicited systemic events

The following systemic events will be solicited:

Table 18 Solicited systemic events

All age groups
Fatigue
Fever
Headache
Muscle ache all over body
Joint pain
Shivering (Chills)
Sweating
Gastrointestinal symptoms: Nausea Vomiting Diarrhea Abdominal pain

Note: participants will be instructed to measure and record the oral body temperature in the evening. Should additional temperature measurements be performed at other times of day, participants will be instructed to record the highest temperature in the diary card.

10.3.4. Unsolicited adverse events

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.

Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, or emergency room visit, or visit to/by a health care provider). The participants will be instructed to contact the site as soon as possible to report MAE(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.

Unsolicited AEs that are not medically attended nor perceived as a concern by participant will be collected during interview with the participants and by review of available medical records at the next visit.

10.3.5. Adverse events of special interest (AESIs)

Potential immune-mediated diseases are the only AESIs that will be collected during the study.

10.3.5.1. 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 the Table 19.

However, the investigator will exercise his/her medical and scientific judgement 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.

Table 19 List of potential immune-mediated diseases (pIMDs) (Amended 22 February 2022)

Medical Concept	*Additional Notes*
Blood disorders and coagulopathies	
Antiphospholipid syndrome	
Autoimmune aplastic anemia	
Autoimmune hemolytic anemia	• ***Includes warm antibody hemolytic anemia and cold antibody hemolytic anemia***
Autoimmune lymphoproliferative syndrome (ALPS)	
Autoimmune neutropenia	
Autoimmune pancytopenia	
Autoimmune thrombocytopenia	• ***Frequently used related terms include: "autoimmune thrombocytopenic purpura", "idiopathic thrombocytopenic purpura (ITP)", "idiopathic immune thrombocytopenia", "primary immune thrombocytopenia".***
Evans syndrome	
Pernicious anemia	

Medical Concept	*Additional Notes*
Thrombosis with thrombocytopenia syndrome (TTS)	
Thrombotic thrombocytopenic purpura	• ***Also known as "Moschcowitz-syndrome" or "microangiopathic hemolytic anemia"***
Cardio-pulmonary inflammatory disorders	
Idiopathic Myocarditis/Pericarditis	***Including but not limited to:*** • ***Autoimmune / Immune-mediated myocarditis*** • ***Autoimmune / Immune-mediated pericarditis*** • ***Giant cell myocarditis***
Idiopathic pulmonary fibrosis	***Including but not limited to:*** • ***Idiopathic interstitial pneumonia (frequently used related terms include "Interstitial lung disease", "Pulmonary fibrosis", "Immune-mediated pneumonitis")*** • ***Pleuroparenchymal fibroelastosis (PPFE)***
Pulmonary alveolar proteinosis (PAP)	• ***Frequently used related terms include: "pulmonary alveolar lipoproteinosis", "phospholipidosis"***
Endocrine disorders	
Addison's disease	
Autoimmune / Immune-mediated thyroiditis	***Including but not limited to:*** • ***Hashimoto thyroiditis (autoimmune hypothyroidism, lymphocytic thyroiditis)*** • ***Atrophic thyroiditis*** • ***Silent thyroiditis*** • ***Thyrotoxicosis***
Autoimmune diseases of the testis and ovary	• ***Includes autoimmune oophoritis, autoimmune ovarian failure and autoimmune orchitis***
Autoimmune hyperlipidemia	
Autoimmune hypophysitis	
Diabetes mellitus type I	
Grave's or Basedow's disease	• ***Includes Marine Lenhart syndrome and Graves' ophthalmopathy, also known as thyroid eye disease (TED) or endocrine ophthalmopathy***
Insulin autoimmune syndrome	
Polyglandular autoimmune syndrome	• ***Includes Polyglandular autoimmune syndrome type I, II and III***
Eye disorders	
Ocular Autoimmune / Immune-mediated disorders	***Including but not limited to:*** • ***Acute macular neuroretinopathy (also known as acute macular outer retinopathy)*** • ***Autoimmune / Immune-mediated retinopathy***

Medical Concept	*Additional Notes*
	• *Autoimmune / Immune-mediated uveitis, including idiopathic uveitis and sympathetic ophthalmia* • *Cogan's syndrome: an oculo-audiovestibular disease* • *Ocular pemphigoid* • *Ulcerative keratitis* • *Vogt-Koyanagi-Harada disease*
Gastrointestinal disorders	
Autoimmune / Immune-mediated pancreatitis	
Celiac disease	
Inflammatory Bowel disease	*Including but not limited to:* • *Crohn's disease* • *Microscopic colitis* • *Terminal ileitis* • *Ulcerative colitis* • *Ulcerative proctitis*
Hepatobiliary disorders	
Autoimmune cholangitis	
Autoimmune hepatitis	
Primary biliary cirrhosis	
Primary sclerosing cholangitis	
Musculoskeletal and connective tissue disorders	
Gout	• *Includes gouty arthritis*
Idiopathic inflammatory myopathies	*Including but not limited to:* • *Dermatomyositis* • *Inclusion body myositis* • *Immune-mediated necrotizing myopathy* • *Polymyositis*
Mixed connective tissue disorder	
Polymyalgia rheumatica (PMR)	
Psoriatic arthritis (PsA)	
Relapsing polychondritis	
Rheumatoid arthritis	*Including but not limited to:* • *Rheumatoid arthritis associated conditions* • *Juvenile idiopathic arthritis* • *Palindromic rheumatism* • *Still's disease* • *Felty's syndrome*
Sjögren's syndrome	

Medical Concept	*Additional Notes*
Spondyloarthritis	*Including but not limited to:* • *Ankylosing spondylitis* • *Juvenile spondyloarthritis* • *Keratoderma blenorrhagica* • *Psoriatic spondylitis* • *Reactive Arthritis (Reiter's Syndrome)* • *Undifferentiated spondyloarthritis*
Systemic Lupus Erythematosus	• *Includes Lupus associated conditions (e.g. Cutaneous lupus erythematosus, Lupus nephritis, etc.) or complications such as shrinking lung syndrome (SLS)*
Systemic Scleroderma (Systemic Sclerosis)	• *Includes Reynolds syndrome (RS), systemic sclerosis with diffuse scleroderma and systemic sclerosis with limited scleroderma (also known as CREST syndrome)*
Neuroinflammatory/neuromuscular disorders	
Acute disseminated encephalomyelitis (ADEM) and other inflammatory-demyelinating variants	*Includes the following:* • *Acute necrotising myelitis* • *Bickerstaff's brainstem encephalitis* • *Disseminated necrotizing leukoencephalopathy (also known as Weston-Hurst syndrome, acute hemorrhagic leuko-encephalitis, or acute necrotizing hemorrhagic encephalomyelitis)* • *Myelin oligodendrocyte glycoprotein antibody-associated disease* • *Neuromyelitis optica (also known as Devic's disease)* • *Noninfective encephalitis / encephalomyelitis / myelitis* • *Postimmunization encephalomyelitis*
Guillain-Barré syndrome (GBS)	• *Includes variants such as Miller Fisher syndrome and the acute motor and sensory axonal neuropathy (AMSAN)*
Idiopathic cranial nerve palsies/paresis and inflammations (neuritis)	*Including but not limited to:* • *Cranial nerve neuritis (e.g. Optic neuritis)* • *Idiopathic nerve palsies/paresis (e.g. Bell's palsy)* • *Melkersson-Rosenthal syndrome* • *Multiple cranial nerve palsies/paresis*
Multiple Sclerosis (MS)	*Includes the following:* • *Clinically isolated syndrome (CIS)* • *Malignant MS (the Marburg type of MS)* • *Primary-progressive MS (PPMS)* • *Radiologically isolated syndrome (RIS)* • *Relapsing-remitting MS (RRMS)* • *Secondary-progressive MS (SPMS)* • *Uhthoff's phenomenon*
Myasthenia gravis	• *Includes ocular myasthenia and Lambert-Eaton myasthenic syndrome*

Medical Concept	*Additional Notes*
Narcolepsy	• *Includes narcolepsy with or without presence of unambiguous cataplexy*
Peripheral inflammatory demyelinating neuropathies and plexopathies	*Including but not limited to:* • *Acute Brachial Radiculitis (also known as Parsonage-Turner Syndrome or neuralgic amyotrophy)* • *Antibody-mediated demyelinating neuropathy* • *Chronic idiopathic axonal polyneuropathy (CIAP)* • *Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP), including atypical CIDP variants (e.g. multifocal acquired demyelinating sensory and motor neuropathy also known as Lewis-Sumner syndrome)* • *Multifocal motor neuropathy (MMN)*
Transverse myelitis (TM)	• *Includes acute partial transverse myelitis (APTM) and acute complete transverse myelitis (ACTM)*
Renal disorders	
Autoimmune / Immune-mediated glomerulonephritis	*Including but not limited to:* • *IgA nephropathy* • *IgM nephropathy* • *C1q nephropathy* • *Fibrillary glomerulonephritis* • *Glomerulonephritis rapidly progressive* • *Membranoproliferative glomerulonephritis* • *Membranous glomerulonephritis* • *Mesangioproliferative glomerulonephritis* • *Tubulointerstitial nephritis and uveitis syndrome*
Skin and subcutaneous tissue disorders	
Alopecia areata	
Autoimmune / Immune-mediated blistering dermatoses	*Including but not limited to:* • *Bullous Dermatitis* • *Bullous Pemphigoid* • *Dermatitis herpetiformis* • *Epidermolysis bullosa acquisita (EBA)* • *Linear IgA-mediated bullous dermatosis (LABD), also known as Linear IgA disease* • *Pemphigus*
Erythema multiforme	
Erythema nodosum	
Reactive granulomatous dermatitis	*Including but not limited to* • *Interstitial granulomatous dermatitis* • *Palisaded neutrophilic granulomatous dermatitis*

Medical Concept	*Additional Notes*
Lichen planus	• *Includes liquen planopilaris*
Localised Scleroderma (Morphoea)	• *Includes Eosinophilic fasciitis (also called Shulman syndrome)*
Psoriasis	
Pyoderma gangrenosum	
Stevens-Johnson Syndrome (SJS)	*Including but not limited to:* • *Toxic Epidermal Necrolysis (TEN)* • *SJS-TEN overlap*
Sweet's syndrome	• *Includes Acute febrile neutrophilic dermatosis*
Vitiligo	
Vasculitis	
Large vessels vasculitis	*Including but not limited to:* • *Arteritic anterior ischemic optic neuropathy (AAION or arteritic AION)* • *Giant cell arteritis (also called temporal arteritis)* • *Takayasu's arteritis*
Medium sized and/or small vessels vasculitis	*Including but not limited to:* • *Anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified)* • *Behcet's syndrome* • *Buerger's disease (thromboangiitis obliterans)* • *Churg–Strauss syndrome (allergic granulomatous angiitis)* • *Erythema induratum (also known as nodular vasculitis)* • *Henoch-Schonlein purpura (also known as IgA vasculitis)* • *Microscopic polyangiitis* • *Necrotizing vasculitis* • *Polyarteritis nodosa* • *Single organ cutaneous vasculitis, including leukocytoclastic vasculitis, hypersensitivity vasculitis and acute hemorrhagic edema of infancy (AHEI)* • *Wegener's granulomatosis*
Other (including multisystemic)	
Anti-synthetase syndrome	
Capillary leak syndrome	• *Frequently used related terms include : "systemic capillary leak syndrome (SCLS)" or "Clarkson's Syndrome"*
Goodpasture syndrome	• *Frequently used related terms include : "pulmonary renal syndrome" and "anti-Glomerular Basement Membrane disease (anti-GBM disease)"*
Immune-mediated enhancement of disease	• *Includes vaccine associated enhanced disease (VAED and VAERD). Frequently used related terms include "vaccine-mediated enhanced disease (VMED)", "enhanced respiratory disease (ERD)", "vaccine-induced enhancement of infection",*

Medical Concept	*Additional Notes*
	"disease enhancement", "immune enhancement", and "antibody-dependent enhancement (ADE)
Immunoglobulin G4 related disease	
Langerhans' cell histiocytosis	
Multisystem inflammatory syndromes	*Including but not limited to:* • *Kawasaki's disease* • *Multisystem inflammatory syndrome in adults (MIS-A)* • *Multisystem inflammatory syndrome in children (MIS-C)*
Overlap syndrome	
Raynaud's phenomenon	
Sarcoidosis	• *Includes Loefgren syndrome*
Susac's syndrome	

10.3.6. Clinical laboratory parameters and other abnormal assessments qualifying as AEs or SAEs

In the absence of a diagnosis, abnormal laboratory findings (e.g. clinical chemistry, hematology, urinalysis) or other abnormal assessments (e.g. physical examination findings) the investigator considers clinically significant will be recorded as an AE or SAE if they meet the definition of an AE or SAE (refer to the Sections 10.3.1 and 10.3.2).

The investigator will exercise his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

10.3.7. Events or outcomes not qualifying as AEs or SAEs

10.3.7.1. Pregnancy

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. Please refer to the Section 10.3.2 for definition of SAE.

10.3.8. Recording and follow-up of AEs, SAEs, pIMDs and pregnancies

The participants will be instructed to contact the investigator immediately should the participants manifest any signs or symptoms they perceive as serious.

When an AE/SAE/pIMD/pregnancy occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE/pIMD/pregnancy in the eCRF. The investigator is not allowed to send photocopies of the participant's medical records to GSK instead of appropriately completing the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all participant identifiers will be blinded on the copies of the medical records prior to submission to GSK.

The investigator will attempt to establish a diagnosis pertaining to the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

A Paper Diary (pDiary), hereafter referred to as Participant Diary will be used in this study to capture solicited administration site or systemic events. The participant should be trained on how and when to complete each field of the Participant Diary.

At each vaccination visit, diary cards will be provided to the participant. The participant will be instructed to measure and record the oral body temperature and any solicited administration site/systemic events (i.e. on the day of vaccination and during the next 6 days) or any unsolicited AEs (i.e. on the day of vaccination and during the next 20 days occurring after vaccination). For solicited events continuing after 7 days, the participant will be instructed to record events until 21 days post-vaccination or until resolution. Solicited events that continue after 7 days will be recorded as an unsolicited AE. The participant will be instructed to return the completed diary card to the investigator at the next study visit or by mail using the pre-stamped envelope received at the site. Details on the timing and collection of the solicited administration site and systemic events on the diary card will be described in the SPM.

At each vaccination visit, a COVID-19 assessment card will be provided to the participant. The participant will be instructed to return the completed assessment card to the investigator at the next study visit or by mail using the pre-stamped envelope received at the site.

In addition, solicited events with a start day after day 7 post-vaccination (e.g. Day 8 after dose 1 and Day 28 after dose 2) will be recorded as unsolicited AEs.

Any individual(s) who performs the measurements of administration site or systemic events and who will enter the information into the Participant Diary should be trained on the use of the Diary. This training must be documented in the participant's source record. If any other individual, the participant is making entries in the Participant Diary, their identity should be documented in the Participant Diary/participant's source record.

- Collect and verify completed diary cards during discussion with the participant on Visit 2 and Visit 3.
- Any unreturned diary cards will be sought from the participant through telephone call(s) or any other convenient procedure.

The investigator or delegate will transcribe the required information into the eCRF in English.

10.3.8.1. Time period for collecting and recording AEs

All AEs that occur within 21 days following administration of each dose of study vaccine/product must be recorded into the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination-related. **(Amended 22 February 2022)**

10.3.8.2. Follow-up of AEs, SAEs, pIMDs or any other events of interest

After the initial AE/SAE/pIMD or any other event of interest for the study, the investigator is required to proactively follow each participant at subsequent visits/contacts. The investigator will follow participants with SAEs, pIMDs (serious or non-serious), or participants withdrawn from the study as a result of an AE, until the event has resolved, subsided, stabilized, disappeared, or until the event is otherwise explained, or the participant is lost to follow-up.

Other non-serious AEs must be followed until the event is resolved, stabilized, otherwise explained or until the participant is lost to follow-up.

10.3.8.2.1. 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 the end of the study.

If participant dies during participation in the study or during a recognized follow-up period, GSK will be provided with any available post-mortem findings, including histopathology.

10.3.8.2.2. Follow-up after the participant is discharged from the study

The investigator will provide any new or updated relevant information on previously reported SAE/pIMD to GSK using a paper/electronic Expedited Adverse Events Report and/or pregnancy report as applicable. The investigator is obliged to perform or arrange for the conduct of supplemental clinical examinations/tests and/or evaluations to elucidate the nature and/or causality of the AE or SAE as fully as possible.

10.3.8.2.3. 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 paper pregnancy follow-up report and the Expedited Adverse Events Report if applicable. Generally, the follow-up period doesn't need to be longer than 6 to 8 weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs for this study, if the pregnancy outcome is an SAE, it should always be reported as an SAE.

Furthermore, in case if the investigator becomes aware of any SAE occurring as a result of a post-study pregnancy AND considered by the investigator to be reasonably related to the study vaccine/product, he/she has to report this information to GSK as described in the Section 10.3.10.

10.3.8.3. Updating of SAE, pIMD and pregnancy information after removal of write access to the participant's eCRF

When additional SAE, pIMD or pregnancy information is received after removal of write access to the participant's eCRF, 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 faxed to the Study Contact for Reporting SAEs (refer to the Section 8.3.3.1) or to GSK Clinical Safety and Pharmacovigilance department within the defined reporting time frames specified in the Table 12.

10.3.9. Assessment of intensity and toxicity

10.3.9.1. Assessment of intensity

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

Table 20 Intensity scales for solicited events in adults 18 years of age or more

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 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.

Adults (≥18 years)		
Event	**Intensity grade**	**Parameter**
	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

* Refer to the SoA (Section 1.3) 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)

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 intensity should be assigned to 1 of the following categories:

1 (mild)	=	An AE which is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevents normal, everyday activities In adults, such an AE would, for example, prevent attendance at work/school and would necessitate the administration of corrective therapy.

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 pre-defined outcomes as described in the Section 10.3.2.

10.3.9.2. Assessment of causality

All solicited administration-site and systemic events will be considered causally related to vaccination. The complete list of these events is provided in the Table 17 and Table 18.

The investigator must assess the relationship between study vaccine/product and the occurrence of each unsolicited AE/SAE using clinical judgement. Where several different vaccines/products were administered, the investigator should specify, when possible, if the unsolicited AE/SAE could be causally related to a specific vaccine/product (i.e. investigational, control/placebo or co-administered vaccine). When causal relationship to a specific vaccine/product cannot be determined, the investigator should indicate the unsolicited AE/SAE to be related to all products.

Alternative plausible causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study vaccine/product will be considered and investigated. The investigator will also consult the IB to determine his/her assessment.

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 10.3.2), 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.
- Lack of efficacy of the vaccine/product, if applicable.
- Erroneous administration.
- Other cause (specify).

There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, it is very important to record an assessment of causality for every event before submitting the Expedited Adverse Events Report to GSK.

The causality assessment is 1 of the criteria used when determining regulatory reporting requirements. The investigator may change his/her opinion of causality after receiving additional information and update the SAE information accordingly.

10.3.9.3. Medically attended visits

For each solicited and unsolicited symptom the participant experiences, the participant will be asked if he/she received medical attention defined as hospitalization, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits. This information will be recorded in the eCRF.

10.3.9.4. Assessment of outcomes

The investigator will assess the outcome of all unsolicited AEs (including SAEs) recorded during the study as:

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

10.3.10. Reporting of SAEs, pIMDs, pregnancies and other events

10.3.10.1. Events requiring expedited reporting to GSK

Once an investigator becomes aware that an SAE has occurred in a study participant, the investigator (or designee) must complete information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS. The report will always be completed as thoroughly as possible with all available details of the event.

Even if the investigator does not have all information regarding an SAE, the report should still be completed within 24 hours. Once additional relevant information is received, the report should be updated WITHIN 24 HOURS. The investigator will always provide an assessment of causality at the time of the initial report.

Refer to the Table 12 for the details on timeframes for reporting of SAEs/pIMDs/pregnancies.

The investigator will be required to confirm the review of the SAE causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE.

Refer to the Section 10.3.10.2 for the back-up system in case the electronic reporting system does not work.

10.3.10.2. Back-up system in case facsimile or electronic reporting system does not work

In rare circumstances if the electronic reporting system does not work, the investigator (or designee) must fax completed, dated and signed paper Expedited Adverse Events Report to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to GSK Clinical Safety and Pharmacovigilance department within 24 hours.

Investigator (or designee) must complete the electronic Expedited Adverse Events Report within 24 hours upon electronic reporting system is resumed. The information reported through the electronic SAE reporting system will be considered valid for regulatory reporting purposes.

10.4. Appendix 4: COVID-19 definition and assessment card

COVID-19 cases will be captured based on the WHO criteria using the following categories: suspected, probable and confirmed cases. These COVID-19 infection cases will be submitted as AEs per normal reporting mechanisms. Investigators will have to use the case definitions provided below [WHO, 2020]. All AEs will have to be considered as to whether they meet SAE criteria, and if so, submitted through the SAE reporting mechanism. The COVID-19 eCRF page will have to be used to capture additional COVID-19 case details that would not normally be contained elsewhere in the eCRF.

Case Definition for COVID-19 Coronavirus Infection

WHO Case Definition (March 27, 2020 Version):

Suspected case

A. A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath), AND 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;

OR

B. A patient with any acute respiratory illness AND having been in contact (see definition of "contact" below) with a confirmed or probable COVID-19 case (see definition of contact) in the last 14 days prior to symptom onset;

OR

C. A patient with severe acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath; AND requiring hospitalization) AND in the absence of an alternative diagnosis that fully explains the clinical presentation.

Probable case

A. A suspect case for whom testing for the COVID-19 virus is inconclusive (Inconclusive being the result of the test reported by the laboratory).

OR

B. A suspect case for whom testing could not be performed for any reason.

Confirmed case

A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.

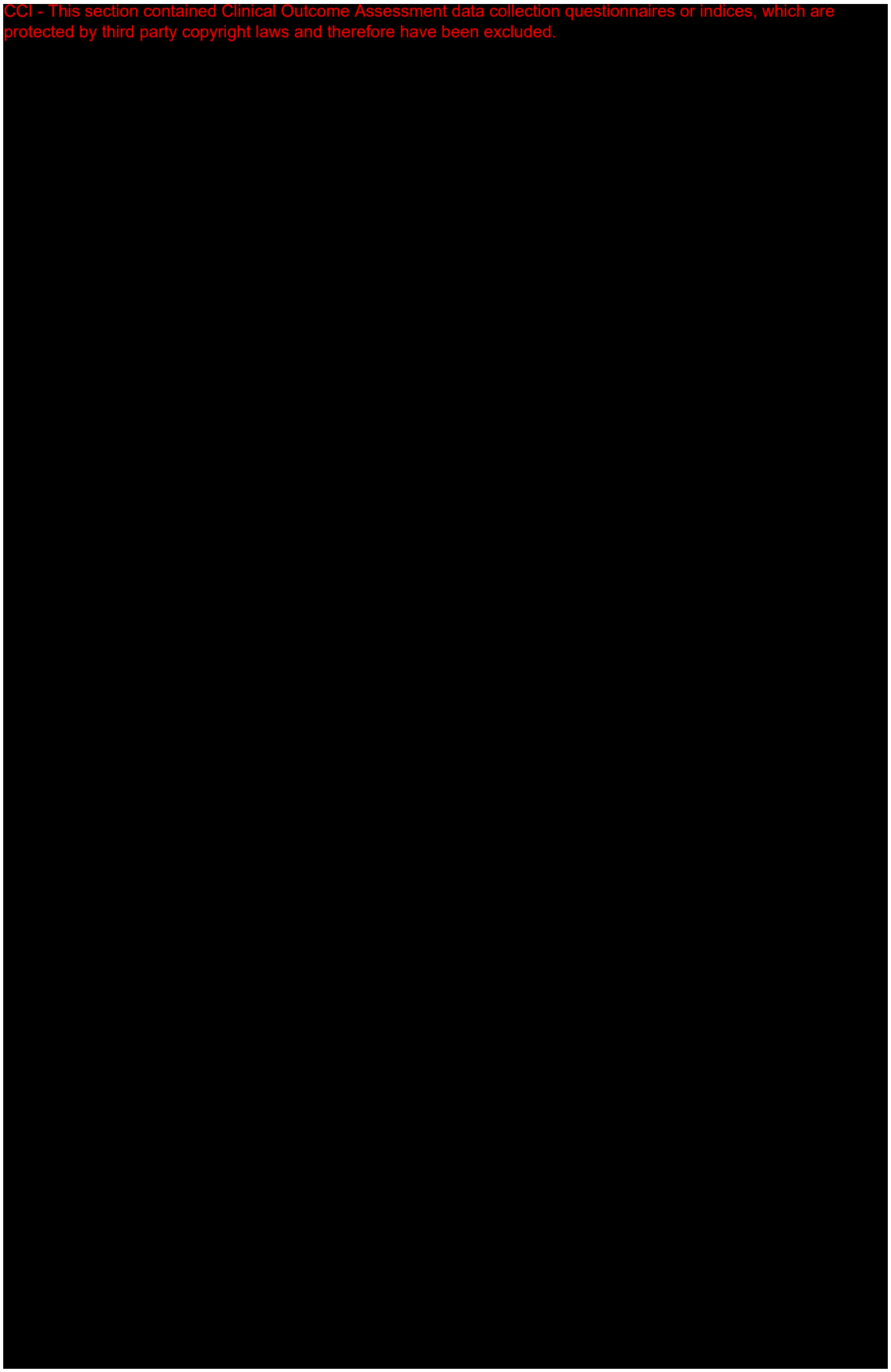
A contact is a person who experienced any one of the following exposures during the 2 days before and the 14 days after the onset of symptoms of a probable or confirmed case:

1. Face-to-face contact with a probable or confirmed case within 1 meter and for more than 15 minutes;
2. Direct physical contact with a probable or confirmed case;
3. Direct care for a patient with probable or confirmed COVID-19 disease without using proper personal protective equipment; OR
4. Other situations as indicated by local risk assessments.

Note: for confirmed asymptomatic cases, the period of contact is measured as the 2 days before through the 14 days after the date on which the sample was taken which led to confirmation.

10.4.1. COVID-19 assessment card

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.



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10.5. Appendix 5: Contraceptive guidance and collection of pregnancy information

10.5.1. Definitions

10.5.1.1. Women of childbearing potential

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

10.5.1.1.1. Women not considered as women of childbearing potential

- Premenarchal

  Menarche is the onset of menses for the first time in a young female and is preceded by several changes associated with puberty including breast development and pubic hair growth.

  If fertility is unclear (e.g. amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

- Premenopausal female with ONE of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

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

- Postmenopausal female

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone 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 follicle stimulating hormone measurement is insufficient.

- Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-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.

10.5.2. Contraception guidance

- Female participants of childbearing potential are eligible to participate if they agree to use an adequate contraception consistently and correctly according to the methods listed in GSK list of highly effective contraceptive methods provided in Table 21.

Table 21 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 • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device • Intrauterine hormone-releasing system • Bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Male partner sterilization prior to the female participant's entry into the study, and this male is the sole partner for that participant, *(The information on the male sterility can come from the site personnel's review of the participant's medical records; medical examination and/or semen analysis, or medical history interview provided by her or her partner).*
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 in clinical studies.

10.5.3. Collection of pregnancy information

10.5.3.1. Female participants who become pregnant

Refer to the Sections 8.3.1, 8.3.2, 10.3.8.1 and 10.3.8.3 for further information on detection, recording, reporting and follow-up of pregnancies.

Any female participant who becomes pregnant during the study will discontinue study intervention.

10.6. Appendix 6: Country-specific requirements

Not applicable

10.7. Appendix 7: Abbreviations and glossary of terms

10.7.1. List of abbreviations

AE:	Adverse event
AESI:	Adverse event of special interest
BARDA:	Biomedical Advanced Research and Development Authority
CBER:	Center for Biologics Evaluation and Research
CI:	Confidence interval
COVID-19:	Coronavirus disease 2019
DIL:	dilution
eCRF:	electronic case report form
ES:	Exposed Set
GCP:	Good Clinical Practice
GMT:	Geometric mean titers
GSK:	GlaxoSmithKline
HA:	Hemagglutinin
HAU:	Hemagglutinin units
HI:	Hemagglutination inhibition
IB:	Investigator Brochure
ICF:	Informed consent form
ICH:	International Council on Harmonisation
IEC:	Independent Ethics Committee
IRB:	Institutional Review Board

IRT:	Interactive Response Technology
iSRC:	Internal Safety Review Committee
LL:	Lower limit
MAE:	Medically attended adverse event
MN:	Microneutralization
MN mPPS:	***Microneutralization modified per protocol set*** **(Amended 22 February 2022)**
MNPPS:	Microneutralization per protocol set
mPPS:	***Modified per protocol set*** **(Amended 22 February 2022)**
pIMD:	Potential Immune-Mediated Disease
PPS:	Per protocol set
SAE:	Serious adverse event
SAP:	Statistical analysis plan
SCR:	Seroconversion rate
SoA:	Schedule of Activities
SPM:	Study Procedures Manual
SPR:	Seroprotection rate
SUSAR:	Serious Unexpected Serious Adverse Reaction
TOC:	Table of Contents
US:	United States
VCSP:	Vaccines Clinical Safety and Pharmacovigilance
VSMB:	Vaccine Safety Monitoring Board
WHO:	World Health Organization

10.7.2. 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 adverse event (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 adverse event. In an observer-blind study, the participant, the site and sponsor personnel involved in the clinical evaluation of the participants are blinded while other study personnel may be aware of the treatment assignment.
Certified copy:	A copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.
Eligible:	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Enrolled:	‘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 the purpose of 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 for the definition of ‘enrolled’ applicable to the study.

Essential documents:	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced
eTrack:	GSK's tracking tool for clinical trials.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per-protocol analysis (see Section 9.3 for details on criteria for evaluability).
Immunological correlate of protection:	A correlate of risk that has been validated to predict a certain level of protection from the targeted endpoint.
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.
Intervention number:	A number identifying an intervention to a participant, according to intervention allocation.
Investigational vaccine/product:	A pharmaceutical form of an active ingredient being tested in a clinical trial, including a product with a marketing authorization when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use. Synonym: Investigational Medicinal Product
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:	Term used throughout the protocol to denote an individual who has been contacted to participate or participates in the clinical study, either as a recipient of the vaccine/product or as a control. Synonym: subject

Participant number:	A unique identification number assigned to each participant who consents to participate in the study.
Primary completion: date:	The date that the final participant was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical trial was concluded according to the pre-specified protocol or was terminated.
Randomization:	Process of random attribution of intervention to participants to reduce selection bias.
Self-contained study:	Study with objectives not linked to the data of another study.
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 post-vaccination follow-up period.
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, at the laboratories and at medico-technical departments involved in the clinical trial).
Study vaccine/product:	Any investigational vaccine/product being tested and/or any authorized use of a vaccine/product/placebo as a reference or administered concomitantly, in a clinical trial that evaluates the use of an investigational vaccine/product.

Sub-cohort:	A group of participants for whom specific study procedures are planned as compared to other participants or a group of participants who share a common characteristic (e.g. ages, vaccination schedule…) at the time of enrollment.
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: Protocol Amendment change history

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

DOCUMENT HISTORY	
Document	Date of Issue
Amendment 2	22 February 2022
Amendment 1	27 August 2020
Original Protocol	13 February 2020

Amendments summary of changes table

Document	Date of issue	Section # and Name	Description of Change	Brief Rationale
Amendment 1	27 August 2020	1.1 Synopsis	The following text was added: ***In addition, this study is also intended to capture COVID-19 cases among study participants based on the WHO criteria (suspected, probable, and confirmed cases).***	Due to the COVID-19 pandemic, GSK anticipates that 209671 (FLU Q-PAN H7N9=AS03-002) may receive cases of suspected or confirmed COVID-19 infections. A standardized approach to case definition, case reporting, and case detail data collection is put in place.
Amendment 1	27 August 2020	1.3 Schedule of Activities (SoA)	The text was modified as follows: Distribution of diary cards ***and COVID-19 assessment card***[5] Return of diary cards ***and COVID-19 assessment card***[5] 5. Diary cards used to capture both solicited administration site and systemic events (Days 1-7 after each vaccination) and unsolicited	To reflect study procedures during special circumstances (COVID-19).

Document	Date of issue	Section # and Name	Description of Change	Brief Rationale
			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 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***.	
Amendment 1	27 August 2020	3. Objectives and Endpoints	This objective/endpoint was moved from secondary to primary: ***Occurrence of pIMDs and SAEs until Month 13***	Changed due to feedback from Regulatory Authorities.
Amendment 1	27 August 2020	4.1 Overall design	The following text was added: ***In addition, this study is also intended to capture COVID-19 cases among study participants based on the WHO criteria [WHO, 2020]: 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 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.***	Due to the COVID-19 pandemic, GSK anticipates that study 209671 (FLU Q-PAN H7N9=AS03-002) will receive cases of suspected or confirmed COVID-19 infections. A standardized approach to case definition, case reporting, and case detail data collection is put in place.
Amendment 1	27 August 2020	5.1 Inclusion criteria for enrollment	The text was modified as follows: 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 ***and COVID-19 assessment card***, return for follow-up visits, ***or return the diary cards and COVID-19 assessment card in a timely manner using the pre-stamped envelope received at the site).***	To reflect study procedures during special circumstances (COVID-19).
Amendment 1	27 August 2020	9.4.3.2 Safety	This endpoint was moved from secondary to primary: ***Occurrence and relationship to vaccination of SAEs and pIMDs until Month 13.***	Changed due to feedback from Regulatory Authorities.
Amendment 1	27 August 2020	9.4.5.2 COVID-19 assessments	The following text was added: ***Frequencies and percentages of participants with suspected, probable, or confirmed COVID-19 cases will be summarized for the ES for each study group, age group, and overall. Additional COVID-19 case details will be presented in data listings.*** ***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***	To reflect additional analyses due to special circumstances (COVID-19).

Document	Date of issue	Section # and Name	Description of Change	Brief Rationale
			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 (eg, 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 9.3.1.*** ***If study procedures are modified due to special circumstances, there may be requirement to conduct analyses that separately describe the data collected during the period of modified study procedures.***	
Amendment 1	27 August 2020	10.3.8 Recording and Follow-up of AEs, SAEs, pIMDS, and pregnancies	The text was modified as follows: The participant will be instructed to return the completed diary card to the investigator at the next study visit ***or by mail using the pre-stamped envelope received at the site***. Details on the timing and collection of the solicited administration site and systemic events on the diary card will be described in the SPM. ***At each vaccination visit, a COVID-19 assessment card will be provided to the participant. The participant will be instructed to return the completed assessment card to the investigator at the next study visit or by mail using the pre-stamped envelope received at the site.***	To reflect study procedures during special circumstances (COVID-19).
Amendment 1	27 August 2020	10.4 Appendix 4: COVID-19 definition and assessment card	The case definition for COVID-19 as defined by WHO was added.	The protocol was amended due to the COVID-19 pandemic and the need for a standardized approach to case definition, case reporting, and case detail data collection.
Amendment 1	27 August 2020	10.4.1 COVID-19 assessment card	A COVID-19 assessment card was added.	The protocol was amended due to the COVID-19 pandemic and the need for a standardized approach to case definition, case reporting, and case detail data collection.

Document	Date of issue	Section # and Name	Description of Change	Brief Rationale
Amendment 1	27 August 2020	10.6.1 List of Abbreviations	Two abbreviations were added: COVID-19, TOC	The protocol was amended due to the COVID-19 pandemic and the need for a standardized approach to case definition, case reporting, and case detail data collection.
Amendment 1	27 August 2020	11. References	The following references were added: ***Food and Drug Administration (FDA). Guidance for Industry, Investigators, and Institutional Review Boards. FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency. July 2020. https://www.fda.gov/media/136238/download. Accessed: 31 JULY 2020*** ***World Health Organization (WHO). Coronavirus disease 2019 (COVID-19) Situation Report – 67. 2020. Available at: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200327-sitrep-67-covid-19.pdf?sfvrsn=b65f68eb_4. Accessed: 31 JULY 2020.***	Reference for the FDA COVID-19 clinical trial guidance and WHO case definition of COVID-19.

Detailed description of Protocol Amendment 2:

Amended text has been included in *bold italics* in the body of the protocol. The amended text (in *bold italics*) and the deleted text (in ~~strikethrough~~**) are provided below:**

<u>Sponsor Signatory Approval</u>

Andrew Hastie ~~Jerome Wilson~~, Clinical and Epidemiology Project Lead, Vaccines for Influenza

Section 8.3.3 Regulatory reporting requirements for SAEs, pregnancies, and other events

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours* ‡	Electronic Expedited Adverse Events Report	24 hours*	Electronic Expedited Adverse Events Report
Pregnancies	***24 hours**** ~~2 weeks~~	Paper pregnancy notification report	***24 hours**** ~~2 weeks~~	Paper pregnancy follow-up report
pIMDs	24 hours** ‡	Electronic Expedited Adverse Events Report	24 hours*	Electronic Expedited Adverse Events Report

Section 9.3 Populations for Analyses

Analysis set	Description
Enrolled	Participant's agreed to participate in a clinical study after completion of the informed consent process. Refer to the Glossary of terms for the definition of 'enrolled'.
Randomized	All participants who were randomized to receive a study vaccine.
Exposed *Set* (ES)	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.
Full Analysis Set (FAS) 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).
FAS 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).
Per Protocol Set (PPS) 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). Major protocol deviations leading to exclusion will be defined in the Statistical Analysis Plan (SAP) and the Study Deviation Rules document and will be finalized prior to the interim analysis defined in Section 9.5. Primary immunogenicity data will be evaluated based on this set.
Modified PPS (mPPS) 1	***The mPPS 1 is a subset of FAS 1. The mPPS 1 includes all FAS 1 participants with no major protocol deviations that led 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 between 18-32 study days. The interval between Visit 2 and Visit 3 will be 14-32 calendar days.*** ***Major protocol deviations leading to exclusion will be defined in the Statistical Analysis Plan (SAP) and the Study Deviation Rules Document and will be finalized prior to the interim analysis defined in Section 9.5.***
PPS 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). Major protocol deviations leading to exclusion will be defined in the SAP and the Study Deviation Rules document and will be finalized prior to the interim analysis defined in Section 9.5. Secondary immunogenicity data will be evaluated based on this set.
mPPS 2	***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 between 18-32 study days.***

Analysis set	Description
	Major protocol deviations leading to exclusion will be defined in the SAP and the Study Deviation Rules document and will be finalized prior to the interim analysis defined in Section 9.5.
Microneutralization (MN)	All participants in the Randomized Set who were also selected to the subset of MN evaluation.
Microneutralization Per Protocol Set (MNPPS) 1	All participants in the MN Set who are also part of the PPS 1.
MN mPPS 1	***All participants in the MN Set who are also part of the mPPS 1.***
MNPPS 2	All participants in the MN Set who are also part of the PPS 2.
MN mPPS 2	***All participants in the MN Set who are also part of the mPPS 2.***

Section 9.4.1 General considerations

Derived and transformed data:

- Immunogenicity (Note: The cut-off value for antibody titer is defined by the laboratory before the analysis and will be specified in the clinical study report).
  - A seronegative participant is a participant whose antibody titer is below the assay cut-off value.
  - A seropositive participant is a participant whose antibody titer is greater than or equal to the assay cut-off value.
  - Seroprotection is defined as an HI antibody titer ≥ 40 1/DIL.
  - SPR is defined as the percentage of participants with an HI antibody titer ≥ 40 1/DIL.
  - Seroconversion 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.
  - Vaccine response 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) is defined as the percentage of participants with vaccine response.
  - The geometric mean titers (GMTs) calculations are performed by taking the anti-log of the mean of the log concentration/titer transformations. Values for the antibody concentrations/titers below the assay cut-off will be assigned half the assay cut-off value 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 ***applicable*** Per Protocol Set (PPS) ***as described in Section 9.3 (Table 16)***. ***Supplementary analyses for primary and secondary HI immunogenicity analyses will be based on the applicable mPPS.*** If the difference between PPS ***1*** and FAS ***1*** is greater than 10%, a second analysis based on the FAS will be performed to complement the PPS analysis.
- The MN immunogenicity analyses will be based on the ***applicable*** Microneutralization Per Protocol Set (MNPPS) ***as described in Section 9.3 (Table 16)***. ***Supplementary analyses for MN immunogenicity analyses will be based on the applicable MN mPPS.***

Section 9.4.2 Participants disposition

Major deviations will be summarized for the ES for each study group, age group, and overall. The reason for elimination from the PPS 1 and PPS 2 ***and mPPS 1 and mPPS 2*** will also be summarized. ***The same will be done for MNPPS 1, MNPPS 2, MN mPPS 1 and MN mPPS 2.***

Section 9.4.3.1 Immunogenicity

Primary immunogenicity analyses will be based on the PPS 1 set.

Supplementary immunogenicity analyses will be based on the mPPS 1 set.

The following aggregate variables will be calculated for each vaccine group for vaccine homologous H7N9 HI antibody titer along with Clopper-Pearson exact two-sided 99.17% CIs:

- SCR at Day 43
- SPR at Day 43

Section 9.4.3.2 Safety

Unsolicited AE endpoints

- Occurrence and relationship to vaccination of unsolicited AEs within 21 days ~~(Day 1 to Day 21, Day 22 to Day 43)~~ after each vaccination.
- Occurrence and relationship to vaccination of AEs with MAEs within 21 days ~~(Day 1 to Day 21, Day 22 to Day 43)~~ after each vaccination.

Section 9.4.4.1 Immunogenicity

The following aggregate variables will be calculated for each vaccine group for vaccine homologous H7N9 HI antibody titer:

- 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

For a subset of participants (MNPPS 1 and MNPPS 2 sets ***and MN mPPS 1 and MN mPPS 2***), the following aggregate variables will be calculated for each vaccine group for vaccine-homologous H7N9 MN antibody titer:

- GMTs at Days 1, 22, and 43
- Seropositivity rates at Days 1, 22, and 43
- VRR at Days 22 and 43

Section 9.4.5.1 Demography and baseline characteristics analyses

Demographic characteristics (age, gender, race, center, height, weight, and ethnicity) will be tabulated per study group for each analysis set, age group and overall as described in the SAP.

The mean of continuous variables (plus range and standard deviation) of the enrolled participants, as a whole and per study group, age group and overall, will be calculated.

The distribution of discrete variables will be tabulated as a whole and per study group, age group and overall as described in the SAP.

The analysis of demographics will be performed separately for the ES ~~for each vaccine dose~~ and for the participants contributing to the PPS ***(and mPPS)*** ~~of each vaccine dose~~.

Demographic characteristics (including but not limited to age, gender, race, height, weight, and ethnicity) will be summarized by group using descriptive statistics:

- For categorical variables such as center, the number and frequency in each category will be provided.
- Number (number of participants in the analysis), mean, median, minimum and maximum, and standard deviation will be provided for continuous data such as age.

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

Section 9.5.1.1 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 collected 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 after each vaccination on as clean as possible data.*** ~~Analyses of unsolicited AEs reported up to the Day 43 visit and cleaned in so far as is possible will be carried out.~~
- Analyses of ~~MAEs,~~SAEs, pIMDs, pregnancies and withdrawals due to AEs collected up to the Day 43 post-vaccination visit will be carried out.
- 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 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.

Section 9.5.1.2 Final analysis (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 ~~the Day 43 visit (~~21 days after each vaccination~~)~~.
- Concomitant medications reported up to ~~the Day 43 visit~~ ***21 days after each vaccination***.
- SAEs, pIMDs, 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.

Section 9.5.2 Statistical consideration for interim analysis

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***, ***S***~~M~~AEs, 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% and a Bonferroni adjustment will be applied to allow simultaneous multiple comparisons of each antigen/adjuvant group. For the primary safety analyses no adjustment for multiple comparisons will be made in each antigen/adjuvant group.

Section 10.3.5.1 Potential immune-mediated diseases

Table 19 List of potential immune-mediated diseases (pIMDs)

Medical Concept	*Additional Notes*
Blood disorders and coagulopathies	
Antiphospholipid syndrome	
Autoimmune aplastic anemia	
Autoimmune hemolytic anemia	• *Includes warm antibody hemolytic anemia and cold antibody hemolytic anemia*
Autoimmune lymphoproliferative syndrome (ALPS)	
Autoimmune neutropenia	
Autoimmune pancytopenia	
Autoimmune thrombocytopenia	• *Frequently used related terms include: "autoimmune thrombocytopenic purpura", "idiopathic thrombocytopenic purpura (ITP)", "idiopathic immune thrombocytopenia", "primary immune thrombocytopenia".*
Evans syndrome	
Pernicious anemia	
Thrombosis with thrombocytopenia syndrome (TTS)	
Thrombotic thrombocytopenic purpura	• *Also known as "Moschcowitz-syndrome" or "microangiopathic hemolytic anemia"*
Cardio-pulmonary inflammatory disorders	
Idiopathic Myocarditis/Pericarditis	*Including but not limited to:* • *Autoimmune / Immune-mediated myocarditis* • *Autoimmune / Immune-mediated pericarditis* • *Giant cell myocarditis*
Idiopathic pulmonary fibrosis	*Including but not limited to:* • *Idiopathic interstitial pneumonia (frequently used related terms include "Interstitial lung disease", "Pulmonary fibrosis", "Immune-mediated pneumonitis")* • *Pleuroparenchymal fibroelastosis (PPFE)*
Pulmonary alveolar proteinosis (PAP)	• *Frequently used related terms include: "pulmonary alveolar lipoproteinosis", "phospholipidosis"*
Endocrine disorders	
Addison's disease	
Autoimmune / Immune-mediated thyroiditis	*Including but not limited to:* • *Hashimoto thyroiditis (autoimmune hypothyroidism, lymphocytic thyroiditis)* • *Atrophic thyroiditis* • *Silent thyroiditis*

Medical Concept	*Additional Notes*
	• *Thyrotoxicosis*
Autoimmune diseases of the testis and ovary	• *Includes autoimmune oophoritis, autoimmune ovarian failure and autoimmune orchitis*
Autoimmune hyperlipidemia	
Autoimmune hypophysitis	
Diabetes mellitus type I	
Grave's or Basedow's disease	• *Includes Marine Lenhart syndrome and Graves' ophthalmopathy, also known as thyroid eye disease (TED) or endocrine ophthalmopathy*
Insulin autoimmune syndrome	
Polyglandular autoimmune syndrome	• *Includes Polyglandular autoimmune syndrome type I, II and III*
Eye disorders	
Ocular Autoimmune / Immune-mediated disorders	*Including but not limited to:* • *Acute macular neuroretinopathy (also known as acute macular outer retinopathy)* • *Autoimmune / Immune-mediated retinopathy* • *Autoimmune / Immune-mediated uveitis, including idiopathic uveitis and sympathetic ophthalmia* • *Cogan's syndrome: an oculo-audiovestibular disease* • *Ocular pemphigoid* • *Ulcerative keratitis* • *Vogt-Koyanagi-Harada disease*
Gastrointestinal disorders	
Autoimmune / Immune-mediated pancreatitis	
Celiac disease	
Inflammatory Bowel disease	*Including but not limited to:* • *Crohn's disease* • *Microscopic colitis* • *Terminal ileitis* • *Ulcerative colitis* • *Ulcerative proctitis*
Hepatobiliary disorders	
Autoimmune cholangitis	
Autoimmune hepatitis	
Primary biliary cirrhosis	
Primary sclerosing cholangitis	
Musculoskeletal and connective tissue disorders	
Gout	• *Includes gouty arthritis*

Medical Concept	*Additional Notes*
Idiopathic inflammatory myopathies	*Including but not limited to:* • *Dermatomyositis* • *Inclusion body myositis* • *Immune-mediated necrotizing myopathy* • *Polymyositis*
Mixed connective tissue disorder	
Polymyalgia rheumatica (PMR)	
Psoriatic arthritis (PsA)	
Relapsing polychondritis	
Rheumatoid arthritis	*Including but not limited to:* • *Rheumatoid arthritis associated conditions* • *Juvenile idiopathic arthritis* • *Palindromic rheumatism* • *Still's disease* • *Felty's syndrome*
Sjögren's syndrome	
Spondyloarthritis	*Including but not limited to:* • *Ankylosing spondylitis* • *Juvenile spondyloarthritis* • *Keratoderma blenorrhagica* • *Psoriatic spondylitis* • *Reactive Arthritis (Reiter's Syndrome)* • *Undifferentiated spondyloarthritis*
Systemic Lupus Erythematosus	• *Includes Lupus associated conditions (e.g. Cutaneous lupus erythematosus, Lupus nephritis, etc.) or complications such as shrinking lung syndrome (SLS)*
Systemic Scleroderma (Systemic Sclerosis)	• *Includes Reynolds syndrome (RS), systemic sclerosis with diffuse scleroderma and systemic sclerosis with limited scleroderma (also known as CREST syndrome)*
Neuroinflammatory/neuromuscular disorders	
Acute disseminated encephalomyelitis (ADEM) and other inflammatory-demyelinating variants	*Includes the following:* • *Acute necrotising myelitis* • *Bickerstaff's brainstem encephalitis* • *Disseminated necrotizing leukoencephalopathy (also known as Weston-Hurst syndrome, acute hemorrhagic leuko-encephalitis, or acute necrotizing hemorrhagic encephalomyelitis)* • *Myelin oligodendrocyte glycoprotein antibody-associated disease* • *Neuromyelitis optica (also known as Devic's disease)* • *Noninfective encephalitis / encephalomyelitis / myelitis* • *Postimmunization encephalomyelitis*

Medical Concept	*Additional Notes*
Guillain-Barré syndrome (GBS)	• *Includes variants such as Miller Fisher syndrome and the acute motor and sensory axonal neuropathy (AMSAN)*
Idiopathic cranial nerve palsies/paresis and inflammations (neuritis)	*Including but not limited to:* • *Cranial nerve neuritis (e.g. Optic neuritis)* • *Idiopathic nerve palsies/paresis (e.g. Bell's palsy)* • *Melkersson-Rosenthal syndrome* • *Multiple cranial nerve palsies/paresis*
Multiple Sclerosis (MS)	*Includes the following:* • *Clinically isolated syndrome (CIS)* • *Malignant MS (the Marburg type of MS)* • *Primary-progressive MS (PPMS)* • *Radiologically isolated syndrome (RIS)* • *Relapsing-remitting MS (RRMS)* • *Secondary-progressive MS (SPMS)* • *Uhthoff's phenomenon*
Myasthenia gravis	• *Includes ocular myasthenia and Lambert-Eaton myasthenic syndrome*
Narcolepsy	• *Includes narcolepsy with or without presence of unambiguous cataplexy*
Peripheral inflammatory demyelinating neuropathies and plexopathies	*Including but not limited to:* • *Acute Brachial Radiculitis (also known as Parsonage-Turner Syndrome or neuralgic amyotrophy)* • *Antibody-mediated demyelinating neuropathy* • *Chronic idiopathic axonal polyneuropathy (CIAP)* • *Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP), including atypical CIDP variants (e.g. multifocal acquired demyelinating sensory and motor neuropathy also known as Lewis-Sumner syndrome)* • *Multifocal motor neuropathy (MMN)*
Transverse myelitis (TM)	• *Includes acute partial transverse myelitis (APTM) and acute complete transverse myelitis (ACTM)*
Renal disorders	
Autoimmune / Immune-mediated glomerulonephritis	*Including but not limited to:* • *IgA nephropathy* • *IgM nephropathy* • *C1q nephropathy* • *Fibrillary glomerulonephritis* • *Glomerulonephritis rapidly progressive* • *Membranoproliferative glomerulonephritis* • *Membranous glomerulonephritis* • *Mesangioproliferative glomerulonephritis*

Medical Concept	*Additional Notes*
	• *Tubulointerstitial nephritis and uveitis syndrome*
Skin and subcutaneous tissue disorders	
Alopecia areata	
Autoimmune / Immune-mediated blistering dermatoses	*Including but not limited to:* • *Bullous Dermatitis* • *Bullous Pemphigoid* • *Dermatitis herpetiformis* • *Epidermolysis bullosa acquisita (EBA)* • *Linear IgA-mediated bullous dermatosis (LABD), also known as Linear IgA disease* • *Pemphigus*
Erythema multiforme	
Erythema nodosum	
Reactive granulomatous dermatitis	*Including but not limited to* • *Interstitial granulomatous dermatitis* • *Palisaded neutrophilic granulomatous dermatitis*
Lichen planus	• *Includes liquen planopilaris*
Localised Scleroderma (Morphoea)	• *Includes Eosinophilic fasciitis (also called Shulman syndrome)*
Psoriasis	
Pyoderma gangrenosum	
Stevens-Johnson Syndrome (SJS)	*Including but not limited to:* • *Toxic Epidermal Necrolysis (TEN)* • *SJS-TEN overlap*
Sweet's syndrome	• *Includes Acute febrile neutrophilic dermatosis*
Vitiligo	
Vasculitis	
Large vessels vasculitis	*Including but not limited to:* • *Arteritic anterior ischemic optic neuropathy (AAION or arteritic AION)* • *Giant cell arteritis (also called temporal arteritis)* • *Takayasu's arteritis*
Medium sized and/or small vessels vasculitis	*Including but not limited to:* • *Anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified)* • *Behcet's syndrome* • *Buerger's disease (thromboangiitis obliterans)* • *Churg–Strauss syndrome (allergic granulomatous angiitis)* • *Erythema induratum (also known as nodular vasculitis)*

Medical Concept	*Additional Notes*
	• ***Henoch-Schonlein purpura (also known as IgA vasculitis)*** • ***Microscopic polyangiitis*** • ***Necrotizing vasculitis*** • ***Polyarteritis nodosa*** • ***Single organ cutaneous vasculitis, including leukocytoclastic vasculitis, hypersensitivity vasculitis and acute hemorrhagic edema of infancy (AHEI)*** • ***Wegener's granulomatosis***
Other (including multisystemic)	
Anti-synthetase syndrome	
Capillary leak syndrome	• ***Frequently used related terms include : "systemic capillary leak syndrome (SCLS)" or "Clarkson's Syndrome"***
Goodpasture syndrome	• ***Frequently used related terms include : "pulmonary renal syndrome" and "anti-Glomerular Basement Membrane disease (anti-GBM disease)"***
Immune-mediated enhancement of disease	• ***Includes vaccine associated enhanced disease (VAED and VAERD). Frequently used related terms include "vaccine-mediated enhanced disease (VMED)", "enhanced respiratory disease (ERD)", "vaccine-induced enhancement of infection", "disease enhancement", "immune enhancement", and "antibody-dependent enhancement (ADE)"***
Immunoglobulin G4 related disease	
Langerhans' cell histiocytosis	
Multisystem inflammatory syndromes	***Including but not limited to:*** • ***Kawasaki's disease*** • ***Multisystem inflammatory syndrome in adults (MIS-A)*** • ***Multisystem inflammatory syndrome in children (MIS-C)***
Overlap syndrome	
Raynaud's phenomenon	
Sarcoidosis	• ***Includes Loefgren syndrome***
Susac's syndrome	

The table below was deleted:

Neuroinflammatory disorders	Musculoskeletal disorders	Skin disorders
• Cranial nerve neuropathy, including paralysis and paresis (e.g. Bell's palsy). • Optic neuritis. • Multiple sclerosis. • Transverse myelitis.	• Systemic lupus erythematosus and associated conditions • Systemic scleroderma (Systemic sclerosis), including: • Diffuse Scleroderma, • CREST syndrome. • Idiopathic inflammatory myopathies, including:	• Psoriasis. • Vitiligo. • Erythema nodosum. • Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis).

• Guillain-Barré syndrome, including Miller Fisher syndrome and other variants. • Acute disseminated encephalomyelitis, including site specific variants e.g.: non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculoneuritis. • Myasthenia gravis, including Lambert-Eaton myasthenic syndrome. • Demyelinating peripheral neuropathies including: • Chronic inflammatory demyelinating polyneuropathy, • Multifocal motor neuropathy, • Polyneuropathies associated with monoclonal gammopathy. • Narcolepsy.	• Dermatomyositis, • Polymyositis. • Anti-synthetase syndrome. • Rheumatoid Arthritis and associated conditions including: • Juvenile Idiopathic Arthritis, • Still's disease, • Polymyalgia rheumatica. • Spondyloarthropathies, including: • Ankylosing Spondylitis, • Reactive Arthritis (Reiter's Syndrome), • Undifferentiated Spondyloarthritis, • Psoriatic Arthritis, • Enteropathic arthritis. • Relapsing Polychondritis. • Mixed Connective Tissue disorder. • Gout.	• Lichen planus. • Sweet's syndrome. • Localized Scleroderma (Morphea).
Vasculitis	Blood disorders	Others
• Large vessels vasculitis including: • Giant Cell Arteritis (Temporal Arteritis), • Takayasu's Arteritis. • Medium sized and/or small vessels vasculitis including: • Polyarteritis nodosa, • Kawasaki's disease, • Microscopic Polyangiitis, • Wegener's Granulomatosis (granulomatosis with polyangiitis), • Churg–Strauss syndrome (allergic granulomatous angiitis or eosinophilic granulomatosis with polyangiitis), • Buerger's disease (thromboangiitis obliterans), • Necrotizing vasculitis (cutaneous or systemic), • Anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified),	• Autoimmune hemolytic anemia. • Autoimmune thrombocytopenia. • Antiphospholipid syndrome. • Pernicious anemia. • Autoimmune aplastic anemia. • Autoimmune neutropenia. • Autoimmune pancytopenia.	• Autoimmune glomerulonephritis including: • IgA nephropathy, • Glomerulonephritis rapidly progressive, • Membranous glomerulonephritis, • Membranoproliferative glomerulonephritis, • Mesangioproliferative glomerulonephritis. • Tubulointerstitial nephritis and uveitis syndrome. • Ocular autoimmune diseases including: • Autoimmune uveitis. • Autoimmune retinitis. • Autoimmune myocarditis. • Sarcoidosis. • Stevens-Johnson syndrome. • Sjögren's syndrome. • Alopecia areata.

• Henoch-Schonlein purpura (IgA vasculitis), • Behcet's syndrome, • Leukocytoclastic vasculitis.		• Idiopathic pulmonary fibrosis. • Goodpasture syndrome. • Raynaud's phenomenon.
Liver disorders	Gastrointestinal disorders	Endocrine disorders
• Autoimmune hepatitis. • Primary biliary cirrhosis. • Primary sclerosing cholangitis. • Autoimmune cholangitis.	• Inflammatory Bowel disease, including: • Crohn's disease, • Ulcerative colitis, • Microscopic colitis, • Ulcerative proctitis. • Celiac disease. • Autoimmune pancreatitis.	• Autoimmune thyroiditis (Hashimoto thyroiditis). • Grave's or Basedow's disease. • Diabetes mellitus type I. • Addison's disease. • Polyglandular autoimmune syndrome. • Autoimmune hypophysitis.

Section 10.3.8.1 Time period for collecting and recording AEs

All AEs that occur within 21 days following administration of each dose of study vaccine/product ~~(Day 1 to Day 21 and Day 22 to Day 43)~~ must be recorded into the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

Section 10.7.1 List of abbreviations

mPPS:	***Modified per protocol set***
MN mPPS:	***Microneutralization modified per protocol set***

Section 11 References

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