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

Primary study intervention and number	GSK's lyophilized formulation of the Herpes Zoster subunit vaccine (GSK1437173A) GSK's FLU D-QIV (Quadrivalent Inactivated Split Virion Influenza Vaccine) (GSK2321138A)
Other study interventions	COVID-19 mRNA-1273 vaccine
eTrack study number and abbreviated title	217670 (ZOSTER-091)
Date of protocol	Final: 3 August 2021
Date of protocol amendment	***Amendment 1 Final: 21 September 2021***
Title	A Phase III, randomized, open-label, controlled, multi-center study to evaluate the immune response and safety of both herpes zoster subunit vaccine in healthy adults aged 50 years and older AND the influenza virus vaccine in healthy adults aged 18 years and older when administered sequentially or co-administered with mRNA-1273 booster vaccination.
Brief title	A study on the immune response and safety of the shingles vaccine and the influenza vaccine when either is given to healthy adults at the same time or following a COVID-19 booster vaccine.

Based on GlaxoSmithKline Biologicals SA Protocol WS v17.2

Protocol Amendment 1 Sponsor Signatory Approval

eTrack study number and abbreviated title	217670 (ZOSTER-091)
Date of protocol	Final: 3 August 2021
Date of protocol amendment	***Amendment 1 Final: 21 September 2021***
Title	A Phase III, randomized, open-label, controlled, multi-center study to evaluate the immune response and safety of both herpes zoster subunit vaccine in healthy adults aged 50 years and older AND the influenza virus vaccine in healthy adults aged 18 years and older when administered sequentially or co-administered with mRNA-1273 booster vaccination.
Sponsor signatory	Agnes Mwakingwe-Omari, Clinical and Epidemiology Project Leader for ZOSTER, Clinical Research & Development - United States, GlaxoSmithKline Biologicals SA
Signature	_____
Date	_____
Sponsor signatory	Jerome Wilson, Clinical and Epidemiology Project Leader for Influenza, Clinical Research & Development - United States, GlaxoSmithKline Biologicals SA
Signature	_____
Date	_____

Note: Not applicable if an alternative signature process (e.g., electronic signature or email approval) is used to get the sponsor approval.

Protocol Amendment 1 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 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.
- That I will comply with the terms of the site agreement.
- To ensure that all persons assisting me with the study are adequately informed about the GSK study intervention and other study-related duties and functions as described in the protocol.
- To supervise any individual or party to whom I have delegated study-related duties and functions conducted at the study site.
- To ensure that any individual or party to whom I have delegated study-related duties and functions conducted at the study site are qualified to perform those study-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.
- To perform no biological assays on the clinical samples other than those described in the protocol or its amendment(s).
- To co-operate with representative(s) of GSK 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 study.
- 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 intervention(s), and more generally about his/her financial ties with the sponsor. GSK will use and disclose the information 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 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 all other documents required by regulatory agencies for this study**.**

eTrack study number and abbreviated title	217670 (ZOSTER-091)
Date of protocol	Final: 3 August 2021
Date of protocol amendment	***Amendment 1 Final: 21 September 2021***
Title	A Phase III, randomized, open-label, controlled, multi-center study to evaluate the immune response and safety of both herpes zoster subunit vaccine in healthy adults aged 50 years and older AND the influenza virus vaccine in healthy adults aged 18 years and older when administered sequentially or co-administered with mRNA-1273 booster vaccination.
Investigator name	_____
Signature	_____
Date	_____

SPONSOR INFORMATION

1. Sponsor

GlaxoSmithKline Biologicals SA (GSK)
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 Serious Adverse Events (SAEs)

Refer to Section 8.3.3.1.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Amendment 1 21 September 2021

This amendment is considered substantial based on the criteria defined in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it significantly impacts the scientific value of the study

Overall rationale for the current Amendment: ***This amendment is intended to modify the dose of each mRNA-1273 booster injection to 50 mcg from 100 mcg.***

List of main changes in the protocol and their rationale:

Section # and title	Description of change	Brief rationale
2.2 Background	Moderna ***has been*** evaluating the use of ***50 µg (half dose) or*** 100 µg ***(full dose)*** of mRNA-1273 as a booster vaccine in participants previously vaccinated with 2 doses of 100 µg mRNA-1273 as a primary series. ***Available data indicates that boosting with half dose of the prototype mRNA-1273 has acceptable safety profile and induces robust neutralization titers against the Wuhan strain and variant viruses tested in all participants [***Wu***, 2021b]. It is however unclear if the half dose will sufficiently boost the immune response against other variants that are expected to emerge as the pandemic continues to evolve. Additional trials are underway to assess the safety and immunogenicity of different dose levels of the booster vaccines e.g.100 µg of mRNA-1273 (clinicaltrials.gov: NCT04889209), as well as newly developed variant-specific vaccines (clinicaltrials.gov: NCT04927065). As of September 14th, 2021, the half dose (50 µg) mRNA-1273 booster is one of the COVID-19 booster vaccines recommended in the UK, to be administered at least 6 months after the primary series for certain populations at higher risk of severe COVID-19 disease. [JCVI 2021] The half dose mRNA-1273 booster is under evaluation by other health agencies such as the European Medicines Agency and the US Food and Drug Administration. (Amended 21 September 2021)***	***Background for consideration of the 50 µg dose of the mRNA-1273 vaccine.***

Section # and title	Description of change	Brief rationale
4.2 Scientific Rationale	As of summer, 2021, vaccines against COVID-19 in people ages 12 years and older have become an essential part of healthcare procedures to control the COVID-19 pandemic. ***With the emergence and spread of the SARS-CoV-2 virus variants that may not be sufficiently controlled by the primary vaccinations,*** periodic administration of booster COVID-19 vaccines after primary vaccination ***is either already recommended for specific populations or is under consideration by various health agencies.***	**Amended to reflect the current regulatory environment.**
4.3 Justification of dose.	Moderna's mRNA-1273 vaccine is authorized for use in the U.S in adults 18 YOA and older under an EUA by the FDA and as a primary series of two 100 µg doses administered 1 month apart. Doses of 100 µg and 50 µg of the same vaccine are being investigated as a potential booster dose to be administered following the primary series. Preliminary results have shown that a 50 µg mRNA-1273 booster dose at least 6 months following the primary series substantially increases neutralizing antibodies against the wildtype SARS-CoV-2 virus and other tested variants, with a safety profile consistent with the known profile in earlier clinical trials [Wu, 2021b]. Currently, in light of the evolving emergence of SARS-CoV-2 variants, it is anticipated that a booster vaccine may be is needed. ***The current available data suggests that 50 µg (half dose) of mRNA-1273 may be sufficient to boost immune response against the existing variants. This half dose is now recommended for boosting in the UK for certain populations at high risk for severe disease, to be administered 6 months post the primary series. This dose is also under review by other health agencies.*** As a result, ***50*** µg of mRNA-1273 will be used in this study. ***To note: If a different dose of mRNA-1273 is approved and recommended for use as a booster in the US while the study is ongoing, the dose of mRNA-1273 booster in the study will be adjusted in the HZ/su and mRNA-1273 booster cohort to the approved dose. The sample size in this cohort will also be adjusted accordingly to ensure sufficient power to achieve the corresponding primary objectives with the adjusted dose. The data generated with the 50 µg of mRNA-1273 booster will then be informative and add to the body of safety and immunogenicity data at this dose level. (Amended 21 September 2021)***	**Justification of Moderna mRNA 1273 booster dose reduction from 100 µg to 50 µg.**

Section # and title	Description of change	Brief rationale
6.3.2 Randomization to study intervention	The stratification by age will be set to target ensure a minimum of 75 participants in the ≥ 65 YOA stratum in each group.	**Due to a later than anticipated start to the study, potential elderly participants may have mostly already received their seasonal influenza vaccines and no longer be eligible.**
9.5.1 Sample size for HZ/su and mRNA-1273 study cohort	***Note: If the dose of mRNA-1273 booster is adjusted while the study is ongoing, the sample size will be compensated in this cohort to ensure that there are enough evaluable participants in each group.***	**Unlike seasonal influenza unpredictability, we would still be able to continue the study and re-estimate sample size requirements for the HZ/su and mRNA-1273 study cohort and make details explicit in a subsequent protocol amendment.**
10.2.6 Adverse Events of Special Interest	***Any case of suspected, probable, or confirmed myocarditis, pericarditis, or myopericarditis should be reported as an AESI, even if it does not meet criteria per the CDC case definition. The event should also be reported as an SAE if it meets any seriousness criterion listed in Section 10.2.2. The following CDC working case definition of myocarditis or pericarditis [Gargano, 2021] is provided as guidance.***	**Text on AESI reporting of myocarditis and pericarditis made consistent with text in other Moderna protocols submitted to IND in past; thereby, also requiring moving from SAE section to AESI section in protocol.**

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

1. PROTOCOL SUMMARY

1.1. Synopsis

Rationale:

The purpose of this study is to evaluate the safety and immunogenicity of GlaxoSmithKline Biologicals SA's (GSK's) herpes zoster (HZ) subunit (su) vaccine (hereafter referred to as HZ/su) and quadrivalent seasonal influenza vaccine (hereafter referred to as Flu D-QIV) when administered sequentially or simultaneously with ModernaTX, Inc.'s (hereby referred to as Moderna) messenger ribonucleic acid (mRNA)-based vaccine booster (hereafter referred to as mRNA-1273 booster) against coronavirus disease 2019 (COVID-19).

Periodic administration of booster vaccines after primary vaccination with COVID-19 vaccines ***are under consideration by various health regulatory agencies*** to combat the possible waning efficacy ***of the primary series*** and the emergence of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) variants. It is therefore important to generate data to support simultaneous administration of mRNA-1273 booster with other routinely recommended vaccines to enhance vaccine coverage rates in the populations at high risk of vaccine-preventable diseases. ***(Amended 21 September 2021)***

Objectives and endpoints:

Refer to Section 3, Table 7.

1.2. Schema

Refer to Section 4.1, Figure 1.

1.3. Schedule of activities (SoA)

Table 1 Schedule of activities

Type of contact		Pre-Vacc	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Phone Contact 1	Phone Contact 2	Notes
Timepoint	HZ/suSeq	-7 days	Day 1	Week 2	Week 4	Week 6	Week 10	Week 14	6 weeks post last dose	24 weeks post last dose	
	HZ/suCoAd			Week 4	Week 8	Week 12					
	FluD-QIVSeq			Week 2	Week 4	Week 6					
	FluD-QIVCoAd			Week 4							
Check inclusion/exclusion criteria		●	○	○	○		○				Applicable eligibility criteria to be checked prior to administering study intervention
Informed consent		●	○								Informed consent to be reconfirmed at Visit 1 and updated in the database if there is a change from what is taken during pre-vaccination visit
Collect demographic data		●									
Medical and vaccination history		●	○								Medical and vaccination history to be updated in the database if there is a change at Visit 1 from what is taken during pre-vaccination visit
History directed physical examination; examine axillae and study intervention administration sites		○	○	○	○	○	○	○			
Check contraindications, warnings and precautions to study intervention administration			○	○	○		○				
Check criteria for temporary delay for study intervention administration			○	○	○		○				
Check criteria for temporary delay for randomization			○								

Type of contact		Pre-Vacc	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Phone Contact 1	Phone Contact 2	Notes
Timepoint	HZ/suSeq	-7 days	Day 1	Week 2	Week 4	Week 6	Week 10	Week 14	6 weeks post last dose	24 weeks post last dose	
	HZ/suCoAd			Week 4	Week 8	Week 12					
	FluD-QIVSeq			Week 2	Week 4	Week 6					
	FluD-QIVCoAd			Week 4							
Urine (or/and blood, as per local requirement) pregnancy test			●	●	●		●				Performed during a vaccination visit, prior o vaccination (see Section 8.2.1.4)
Body temperature before study intervention administration			●	●	●		●				The preferred location for measuring temperature will be the oral route
Randomization			●								
Treatment number allocation			●	●	●		●				
Study intervention administration			Refer to Table 2 for the schedule for each group (●)								
Observation for at least 30 minutes post-study intervention administration			Refer to Table 2 for the schedule for each group (●)								
Recording of administered study treatment number			Refer to Table 2 for the schedule for each group (●)								
Distribution of eDiaries and training participants to use			○	○	○	○	○				
Blood sampling for antibody determination			Refer to Table 2 for blood sampling schedule for each group (●)								
HZ lesion sample (HZ/su and mRNA-1273 booster cohort only)		*Unscheduled visits* (●)									Refer to Table 3 for procedures to be followed
Record any concomitant medications/vaccinations			●	●	●	●	●	●	●	●	
Record any intercurrent medical conditions (IMC)			●	●	●	●	●	●	●	●	
Phone contact for safety follow-up									●	●	

Type of contact		Pre-Vacc	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Phone Contact 1	Phone Contact 2	Notes
Timepoint	HZ/suSeq	-7 days	Day 1	Week 2	Week 4	Week 6	Week 10	Week 14	6 weeks post last dose	24 weeks post last dose	
	HZ/suCoAd			Week 4	Week 8	Week 12					
	FluD-QIVSeq			Week 2	Week 4	Week 6					
	FluD-QIVCoAd			Week 4							
Training participants to recognize signs and symptoms of HZ (HZ/su and mRNA-1273 booster cohort only)			○	○	○	○	○	○			
Recording of solicited AEs: onset post-study intervention administration (day of and following 6 days)			Refer to Table 2 for the schedule for each group (●)								
Review/Return of eDiary			○	○	○	○	○	○			
Recording of non-serious AEs within 30 days post-dosing			●	●	●	●	●	●			
Recording of SAEs, AESIs, COVID-19 cases, and pregnancies. In addition, pIMDs and suspected HZ episodes in the HZ/su and mRNA-1273 booster cohort			●	●	●	●	●	●	●	●	
Recording of AEs/SAEs related to study participation, or SAEs related to concurrent GlaxoSmithKline medication/vaccine		●	●	●	●	●	●	●	●	●	To be recorded if the event onset occurs any time after signing the ICF
Recording of withdrawals			●	●	●	●	●	●	●	●	
Study Conclusion										●	

AE = adverse event; AESI = adverse event of special interest eDiary = electronic diary; HZ= Herpes Zoster; IMC = intercurrent medical condition; PCR = polymerase chain reaction; pIMD = potential immune mediated disease; SAE = serious adverse event

Grey cells indicate the given activity is not planned for the corresponding timepoint(s)

The double-line border following Phone contact 1 indicates an interim analysis

● is used to indicate a study procedure that requires documentation in the individual electronic case report form

○ is used to indicate a study procedure that does not require documentation in the individual electronic case report form

Table 2 Schedule of study intervention administration and blood sampling for the study groups

Study Groups	Activity	Day 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14
HZ/suSeq	Vaccination	mRNA-1273 booster (right deltoid)	HZ/su (left deltoid)	-	-	-	HZ/su (left deltoid)	-	-
	Blood Draw	15 mL	15 mL	15 mL	15 mL	-	-	-	15 mL
HZ/suCoAd	Vaccination	mRNA-1273 booster (right deltoid) and HZ/su (left deltoid)	-	-	-	HZ/su (left deltoid)	-	-	-
	Blood Draw	15 mL	-	15 mL	-	-	-	15 mL	-
FluD-QIVSeq	Vaccination	mRNA-1273 booster (right deltoid)	Flu D-QIV (left deltoid)	-	-	-	-	-	-
	Blood Draw	15 mL	15 mL	15 mL	15 mL	-	-	-	-
FluD-QIVCoAd	Vaccination	mRNA-1273 booster (right deltoid) and Flu D-QIV (left deltoid)	-	-	-	-	-	-	-
	Blood Draw	15 mL	-	15 mL	-	-	-	-	-

Preferred vaccination sites are listed in the table.
Notes: Refer to Figure 1 for the schedule for each of the study groups. Blood sampling to be completed prior to study intervention administration.

Table 3 Study procedures to be performed during the follow-up period for each suspected HZ episode

Type of contact	Visit HZ-1	Contact HZ-2	Contact HZ-3	Contact HZ-4	Contact HZ-5	Contact HZ-6	Contact HZ-7#
Timepoints	**Day HZ-1**	**Day HZ-8**	**Day HZ-15**	**Day HZ-22**	**Day HZ-29^**	**Day HZ-43**	**Day HZ-57#**
Perform clinical examination	○						
Recording of the HZ onset date by study staff/investigator	●						
Collect HZ lesion samples* (3 replicate samples) for confirmation by PCR of a case of clinically diagnosed suspected HZ	●						
Record detailed relevant clinical information including progression of the HZ case in eCRF by study staff/investigator	●	●	●	●	●	●	●
Record information regarding HZ related complications	●	●	●	●	●	●	●
Record concomitant medication/vaccination	●	●	●	●	●	●	●
Record any other IMCs	●	●	●	●	●	●	●
Record any medical attention received for HZ or any HZ related complication**	●	●	●	●	●	●	●

eCRF = electronic case report form; HZ= Herpes Zoster; IMC = intercurrent medical condition; PCR= Polymerase Chain reaction
Grey cells indicate the given activity is not planned for the corresponding timepoint(s)
● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF.
*If during clinical evaluation at Visit HZ-1, the investigator determines that adequate rash samples are not present (that is <3 lesions present or only papules), the investigator has the option of collecting 3 additional samples, preferably within 7 days.
**Complications of the HZ episode (for example, PHN, disseminated HZ, ophthalmic disease) should be recorded as AE/SAE, as appropriate
^Participants with suspected HZ to be followed up at least till Day HZ 29
Phone contacts to continue once every 2 weeks till the rash is resolved. At the time of Last Participant Last Visit, if a participant has an ongoing HZ episode, they will be followed up till Day HZ-29. The investigator will note in the participant's eCRF the end date of HZ rash and if any HZ-associated symptoms are still ongoing.

Table 4 Intervals between study visits for HZ/su and mRNA-1273 booster cohort

Interval	Planned Visit Interval	Allowed Interval Range*
For HZ/suSeq group		
Pre-vaccination → Visit 1	-7 days	-14 days to Day 1
Visit 1→Visit 2	14 days	14-21 days*
Visit 1→Visit 3	28 days	25-35 days*
Visit 2→Visit 4	28 days	25-35 days*
Visit 2→Visit 5	56 days	49-83 days*
Visit 5→Visit 6	28 days	25-35 days*
Visit 5→Phone contact 1	42 days	42-49 days
Visit 5→Phone contact 2	168 days	154-182 days
For HZ/suCoAd group		
Pre-vaccination → Visit 1	-7 days	-14 days to Day 1
Visit 1→Visit 2	28 days	25-35 days*
Visit 1→Visit 3	56 days	49-83 days*
Visit 3→Visit 4	28 days	25-35 days*
Visit 3→Phone contact 1	42 days	42-49 days
Visit 3→Phone contact 2	168 days	154-182 days

*Participants may not be eligible for the HZ/su and mRNA-1273 Per Protocol Set (PPS) if the visits happen beyond this interval. Intervals between visits and phone contact do not affect HZ/su and mRNA-1273 PPS eligibility.

Table 5 Intervals between study visits for Flu D-QIV and mRNA-1273 booster cohort

Interval	Planned Visit Interval	Allowed Interval Range*
For FluD-QIVSeq group		
Pre-vaccination → Visit 1	-7 days	-14 days to Day 1
Visit 1→Visit 2	14 days	14-21 days*
Visit 1→Visit 3	28 days	25-35 days*
Visit 2→Visit 4	28 days	25-35 days*
Visit 2→Phone contact 1	42 days	42-49 days
Visit 2→Phone contact 2	168 days	154-182 days
For FluD-QIVCoAd group		
Pre-vaccination → Visit 1	-7 days	-14 days to Day 1
Visit 1→Visit 2	28 days	25-35 days*
Visit 1→Phone contact 1	42 days	42-49 days
Visit 1→Phone contact 2	168 days	154-182 days

*Participants may not be eligible for the Flu D-QIV and mRNA-1273 PPS if the visits happen beyond this interval. Intervals between visits and phone contact do not affect Flu D-QIV and mRNA-1273 PPS eligibility.

2. INTRODUCTION

2.1. Study rationale

The purpose of this study is to evaluate the safety and immunogenicity of GSK's HZ/su and Flu D-QIV when administered sequentially or simultaneously with Moderna's mRNA-1273 booster against COVID-19.

Periodic administration of booster vaccines after primary vaccination with COVID-19 vaccines ***are under consideration by various health regulatory agencies*** to combat the possible waning efficacy ***of the primary series*** and the emergence of SARS-CoV-2 variants. It is therefore important to generate data to support simultaneous administration of mRNA-1273 booster vaccine with other routinely recommended vaccines to enhance vaccine coverage rates in the populations at high risk of vaccine-preventable diseases. ***(Amended 21 September 2021)***

2.2. Background

Varicella zoster virus (VZV) causes 2 distinct diseases, varicella (chickenpox) that occurs shortly after primary VZV infection and is characterized by systemic illness and a widely disseminated rash, and HZ (shingles) that occurs when VZV reactivates from latency and typically manifests as a localized, dermatomal rash.

The typical HZ rash usually lasts 2 to 4 weeks accompanied by pain and pruritus. The most common complication of HZ is post-herpetic neuralgia (PHN), an ongoing and often debilitating pain that may persist for months or years [Johnson, 2010]. Other complications may include sight-threatening ocular involvement, neurologic disease, and cutaneous bacterial superinfection. About half of all HZ cases occur in individuals over the age of 60, and individuals who reach 85 YOA have a 50% chance of having HZ during their lifetime. Since the loss of VZV-specific T-cell responses as a result of aging is associated with a heightened susceptibility to HZ, vaccination plays an important role to reduce the risk of HZ in older adults.

GSK's HZ vaccine (commercially available as *Shingrix*) is a non-live, recombinant subunit vaccine and consists of the VZV-glycoprotein E (gE) as an active ingredient, together with the liposome-based adjuvant system (AS) 01_B ($AS01_B$). The liquid AS is used to reconstitute the lyophilized antigen immediately prior to administration. The $AS01_B$ consists of the immunostimulants MPL (3-*O*-desacyl-4'-monophosphoryl lipid A) and QS-21 (a saponin molecule purified from the bark extract of the *Quillaja saponaria* Molina tree), which are formulated in liposomes. HZ/su has been evaluated in older adults (≥50 YOA) and in adults (≥18 YOA) who are immunodeficient or immunosuppressed due to disease or therapy and was shown to be highly efficacious, elicit strong cellular and humoral immune responses and the reactogenicity and safety profile of the vaccine was acceptable [Bastidas, 2019, Cunningham, 2018; Cunningham, 2016; Dagnew, 2019; Lal, 2015; López-Fauqued, 2019; López-Fauqued, 2021]. *Shingrix* is indicated in the U.S. for prevention of HZ in adults aged 50 years and older and in adults aged 18 years and older who are or will be at increased risk of HZ due to immunodeficiency or immunosuppression caused by known disease or therapy.

Influenza is an acute, highly contagious, respiratory disease caused by influenza viruses. There are 2 significant types of influenza (flu) virus that cause disease in humans: Types A and B. The influenza A and B viruses that routinely spread in people (human influenza viruses) are responsible for seasonal flu epidemics each year. Influenza is mainly spread through respiratory droplets and more significantly impacts older people, young children and people with underlying medical conditions. The illness is accompanied by fever and variable degrees of other systemic symptoms, ranging from mild fatigue to respiratory failure and death. Due to frequent genetic and antigenic changes in influenza viruses, seasonal vaccines are frequently reformulated with updated viral strains based on annual World Health Organization (WHO) recommendations. Annual influenza vaccination is an effective measure to reduce the risk of influenza infection and its complications.

GSK's Flu D-QIV (commercially available as *Fluarix Quadrivalent*) is indicated in the U.S. for active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine and is approved for use in persons aged 6 months and older.

COVID-19 is caused by SARS-CoV-2 [Hu, 2020]. As of 26 July 2021, >194 million confirmed cases and >4 million deaths have been reported to the WHO [WHO, 2021].

Individuals >60 YOA with comorbidities are more likely to acquire severe respiratory disease requiring hospitalization. The pathogenesis of SARS-CoV-2 is still unfolding. COVID-19 is characterized by lymphopenia (and lymphocyte exhaustion) with cytokine storm seen in severe disease. A significant decrease in T-cells (including CD4+ and CD8+ T-cells), NK-cells and B-cells has been reported. It has been suggested that COVID-19 may result in impaired immune responses (either due to stress or lymphopenia), which may also trigger VZV reactivation and development of HZ [CDC, 2021b; Cao, 2020; Wang, 2020; Tufan, 2020; Elsaie, 2020; Lee, 2021; Diez-Domingo, 2021].

There are reports that SARS-CoV-2 re-infection can occur suggesting the potential need for re-immunization. In addition, the recent emergence of SARS-CoV-2 variants (such as-501Y.V1 [B.1.17] in the United Kingdom, 501Y.V2 [B.1.351] in South Africa, B.1.617.2 [Delta] in India, etc.) with higher transmission abilities have led to higher reports of COVID-19 cases. Preliminary data indicate that there may be a decrease in efficacy of the current existing vaccines against some emerging variants. A high vaccine coverage is needed to curb transmission and subsequent development of SARS-CoV-2 variants [Fontanet, 2021; Dougherty, 2021].

Moderna's mRNA-1273 COVID-19 vaccine is a novel mRNA-based vaccine encapsulated in a lipid nanoparticle (LNP) against SARS-CoV-2. The vaccine includes a single mRNA sequence encoding the pre-fusion stabilized Spike (S) protein of SARS-CoV-2 (Wuhan strain). Two doses of 100 µg mRNA-1273 showed 94.1% efficacy at preventing COVID-19, including severe disease, and no safety concerns were identified [Baden, 2021;]. The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use for active immunization to prevent COVID-19 in individuals 18 YOA and older. The duration of vaccine efficacy, impact of new SARS-CoV-2 variants on vaccine efficacy, and persistence of immunogenicity are still under investigation [Pegu, 2021; Doria-Rose, 2021; Wu, 2021a].

Moderna ***has been*** evaluating the use of ***50 µg (half dose) or*** 100 µg ***(full dose)*** of mRNA-1273 as a booster vaccine in participants previously vaccinated with 2 doses of 100 µg mRNA-1273 as a primary series. ***Available data indicates that boosting with half dose of the prototype mRNA-1273 has acceptable safety profile and induces robust neutralization titers against the Wuhan strain and variant viruses tested in all participants [Wu, 2021b]. It is however unclear if the half dose will sufficiently boost the immune response against other variants that are expected to emerge as the pandemic continues to evolve. Additional trials are underway to assess the safety and immunogenicity of different dose levels of the booster vaccines e.g.100 µg of mRNA-1273 (clinicaltrials.gov: NCT04889209), as well as newly developed variant-specific vaccines (clinicaltrials.gov: NCT04927065).***

As of September 14th, 2021, the half dose (50 µg) mRNA-1273 booster is one of the COVID-19 booster vaccines recommended in the UK, to be administered at least 6 months after the primary series for certain populations at higher risk of severe COVID-19 disease. [JCVI, 2021] The half dose mRNA-1273 booster is under evaluation by other health agencies such as the European Medicines Agency and the US Food and Drug Administration. (Amended 21 September 2021)

Please refer to the current Investigator's Brochure (IB) for information regarding pre-clinical and clinical studies of *Shingrix* and *Fluarix Quadrivalent* and mRNA-1273.

2.3. Benefit/Risk assessment

2.3.1. Risk assessment and mitigation

Detailed information about the known and expected benefits and risks and expected adverse events (AEs) following administration of HZ/su, Flu D-QIV, and mRNA-1273 vaccines can be found in their respective IBs. The important potential/identified risks and the mitigation strategy associated with study interventions and study procedures are listed in Table 6.

Table 6 Risks associated with study interventions and study procedures and risk mitigation strategies

Important Potential/Identified Risk	Data/Rationale for Risk	Mitigation Strategy
Study intervention: HZ/su		
Risk of potential immune-mediated diseases (pIMDs) following administration of HZ/su	pIMDs are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurological disorders of interest which may or may not have an autoimmune etiology. To date, there is no evidence of an increased risk of pIMDs following vaccination with HZ/su in evaluated adults 50 YOA or older [López-Fauqued, 2019]. Based on the theoretical concern that vaccination with an adjuvanted vaccine containing potent immunostimulants may interfere with immunological self-tolerance, pIMDs undergo special safety monitoring for all GSK vaccines containing Adjuvant Systems.	Close monitoring of pIMDs will be conducted per study protocol and analysis of safety data generated through clinical trials and other sources. The potential risk of events of possible autoimmune etiology to occur is mentioned in the ICF. In addition, the ICF advises participants to contact the study doctor or study staff immediately, should any symptoms be considered of concern. pIMDs will be collected up to study end in HZ/su recipients.
Guillain-Barré Syndrome (GBS)	New available information on GBS emerged from a post-marketing observational study where the risk of GBS following vaccination with HZ/su was assessed in adults aged 65 YOA or older enrolled in the Medicare health insurance in the US. An increased risk of GBS during the 42 days following vaccination was estimated as an excess of 3.13 cases per million doses administered. Based on the review of the accumulated body of the information that is currently available, GSK considers that the strength of the collective evidence is insufficient to determine a causal relationship between HZ/su vaccination and GBS, owing to substantial limitations and confounding variables.	Close monitoring of GBS will be conducted per study protocol and analysis of safety data generated through clinical trials and other sources as part of pIMDs (including GBS). The potential risk of events of possible autoimmune etiology to occur is mentioned in the ICF. In addition, the ICF advises participants to contact the study doctor or study staff immediately, should any symptoms be considered of concern. pIMDs (including GBS) will be collected up to study end.
Hypersensitivity reactions (including anaphylaxis)	Hypersensitivity reactions may occur following exposure to allergens from a variety of sources including food, aeroallergens, venom, drugs and immunizations. Vaccines are a mixture of compounds and allergic sensitization can occur to any	Administration of the study intervention is to be preceded by a review of the participant's medical history (especially with regard to previous vaccination and possible occurrence of undesirable

Important Potential/Identified Risk	Data/Rationale for Risk	Mitigation Strategy
	component. While cutaneous reactions, such as rash or urticaria, are common, anaphylactic reactions are very rare [Ruggeberg, 2007].	events) and a history-directed clinical examination. Anaphylaxis following vaccine administration is a contraindication to subsequent vaccination. As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the study intervention. The onset of serious vaccine-related allergic symptoms is typically immediate. In order to assess and adequately treat participants who may have an allergic reaction to the study intervention, all participants will need to remain under observation (i.e. visibly followed; no specific procedure required) at the study clinic site for at least 30 minutes after each study intervention dose is administered.
Study Intervention: Flu D-QIV		
Anaphylaxis	Anaphylaxis is an acute, severe, multiorgan system reaction that can progress rapidly and be potentially fatal. It may occur following exposure to a variety of allergens, such as food, drugs, insect stings and vaccines. The most commonly involved organ systems include the respiratory, cardiovascular, cutaneous, and gastrointestinal systems. Signs and symptoms can include generalized urticaria, wheezing, swelling of the mouth and throat, difficulty breathing, vomiting, hypotension, decreased level of consciousness, and shock [CDC, 2010; Mustafa, 2012; Ruggeberg, 2007].	Hypersensitivity after previous administration of Flu D-QIV or influenza vaccines or to any component of the vaccine is a contraindication. It is general medical practice to observe patients for 30 minutes following vaccination for signs and symptoms of anaphylaxis. As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following administration of the vaccine. Treatment given for anaphylaxis may include epinephrine, steroids, volume replacement therapy, and antihistamines [Ruggeberg, 2007].

Important Potential/Identified Risk	Data/Rationale for Risk	Mitigation Strategy
GBS	Progressive, bilateral, relatively symmetric flaccid paralysis, which develops over the course of hours or days up to 3 to 4 weeks, is the hallmark of GBS. The respiratory muscles including the diaphragm can be affected, and acute respiratory failure occurs in 25% of patients [Yuki, 2012]. Sensory abnormalities and autonomic dysfunction can also occur [Haber, 2009]. Since launch, 83 cases of GBS were received corresponding to a spontaneous reporting frequency of 0.03 cases per 100,000 doses distributed. Risk window generally highest within 6-8 weeks after potential exposure.	GBS is listed as rare adverse reaction in the labelling. There is no known prevention for GBS. Prompt initiation of plasmapheresis or immunoglobulin infusion may reduce disease severity and speed recovery. The ICF advises participants to contact the study doctor or study staff immediately, should any symptoms be considered of concern.
Bell's Palsy	Abrupt onset of unilateral facial weakness or complete paralysis of all the muscles on one side of the face, dry eye, pain around the ear, an altered sense of taste, hyperacusis (hypersensitivity to sounds), or decreased tearing [Greco, 2012]. Most cases are idiopathic. Known associations with human immunodeficiency virus (HIV) infection, Lyme disease, sarcoidosis, Sjögren's syndrome, acute otitis media, tumor, hypertension, diabetes mellitus, and trauma. Pregnancy and certain viral illnesses (especially herpes viruses) can also be associated with Bell's palsy. Since launch, thirty-six (36) cases including the MedDRA PT term of facial paralysis or facial paresis were received, corresponding to a spontaneous reporting frequency of 0.01cases per 100,000 doses distributed.	As the mechanism of action is not well-understood, there is no known way to prevent Bell's palsy. Most cases resolve, either spontaneously (71%) [Greco, 2012] or with treatment. The ICF advises participants to contact the study doctor or study staff immediately, should any symptoms be considered of concern.
Study intervention: mRNA-1273		
Anaphylaxis	These reactions are very rare and are estimated to occur once per 450,000 vaccinations for vaccines that do not contain allergens such as gelatin or egg protein [Zent, 2002]. Anaphylaxis	As a precaution, all participants will remain under observation at the study site for at least 30 minutes after study intervention administration with medical attention available in case of anaphylaxis.

Important Potential/Identified Risk	Data/Rationale for Risk	Mitigation Strategy
	has been reported following administration of mRNA-1273 vaccine in the general public after Emergency Use Authorization.	
Vasovagal syncope	Vasovagal or anxiety reactions such as syncope can occur before or after any vaccination, is usually triggered by the pain or anxiety caused by the injection and is not related to the substance injected.	Study intervention will be administered with the participant in a seated position by a trained professional. As a precaution, all participants will remain under observation at the study site for at least 30 minutes after study intervention administration with medical attention available in case of vasovagal reactions.
Intramuscular injection containing SM-102 lipid formulation	Intramuscular injection with other mRNA vaccines manufactured by Moderna. containing the SM-102 lipid formulation commonly results in a transient and self-limiting local inflammatory reaction. This typically includes pain, erythema (redness), or swelling (hardness) at the injection site, which are mostly mild-to-moderate in severity and usually occur within 24 hours of vaccination. More severe, but self-limited, local reactions, erythema and induration, have been observed at dose of mRNA-1273 exceeding the dose proposed in this study. Most systemic adverse events observed after vaccination do not exceed mild-to-moderate severity. The most commonly reported systemic adverse reactions (ARs) are anticipated to be fever, fatigue, chills, headache, myalgias and arthralgias. More severe reactions, including erythema, induration, fever, headache and nausea, were reported after receiving doses of mRNA-1273 that were greater than the dose proposed for use in this study. In all cases, the reactions resolved spontaneously.	The participants will be monitored for solicited AEs (Days 1-7) and unsolicited AEs (Days 1-30) following study intervention administration according to the protocol. The ICF advises participants to contact the study doctor or study staff immediately, should any symptoms be considered of concern

Important Potential/Identified Risk	Data/Rationale for Risk	Mitigation Strategy
Vaccine-associated disease enhancement	There is a theoretical risk that active vaccination to prevent the novel viral infection caused by SARS-CoV-2 may cause a paradoxical increase in the risk of disease. This possibility is based on the rare phenomenon of vaccine-associated disease enhancement which was first seen in the 1960s with 2 vaccines made in the same way (formalin-inactivated whole virus) and designed to protect children against infection with RSV [Chin, 1969] or measles [Fulginiti, 1967]. Disease enhancement has also been proposed as a possible explanation for cases of more serious disease associated with dengue vaccination [Thomas, 2019; WHO, 2018]. In Study P301, prespecified harm rules designed to detect an imbalance in cases of COVID-19 or severe COVID-19 were not met. Most importantly, after a median follow-up of 2 months after the second dose of vaccine, the majority of COVID-19 cases occurred in participants who received placebo rather than mRNA-1273 [Baden, 2021], confirming no clinical evidence for vaccine-enhanced disease following vaccination with mRNA-1273.	Available data so far since the vaccine received EUA do not indicate vaccine-associated disease enhancement as a safety concern. Participant's safety data will be monitored as per protocol and will include suspected COVID-19 cases.
Myocarditis or Pericarditis	In the context of the EUA for individuals 18 and older for mRNA-1273, there have been very rare reports of myocarditis and pericarditis occurring after vaccination with Moderna COVID-19 Vaccine. Although causality has not been established, the majority of the cases have been reported in young males shortly after the second dose of the vaccine. These are typically mild cases and individuals tend to recover within a short time following standard treatment and rest [Gargano, 2021].	The ICF advises study participants about the symptoms of myocarditis and pericarditis, and to seek medical attention and contact the study doctor or study staff should any of these symptoms occur following study intervention administration.

Important Potential/Identified Risk	Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Risk from blood sampling	Blood sampling associated risk of discomfort, syncope, dizziness, infection at the site after or during venipuncture.	Blood samples will be obtained in seated or supine position by a trained professional and medical assistance will be available. The potential risk of feeling faint, or experiencing mild local pain, bruising, irritation or redness at the site where blood was taken, is mentioned in the ICF. The amount of blood to be taken for sampling will not be harmful to the participant's health.
Risk of lesion sampling (For HZ/su and mRNA-1273 booster cohort only)	Swab/needle sampling of lesions/crusts associated risk of secondary infection, and discomfort related to the procedure.	Lesion samples will be obtained by a trained professional under aseptic conditions to minimize the potential for secondary infection. The potential risk of some temporary discomfort during the sampling procedure and the risk of infection are mentioned in the ICF.

2.3.2. Benefit assessment

Symptoms directed physical examinations and clinical assessments that the participants will undergo during the study, will be made by trained clinical staff and can provide participants with valuable knowledge about their health (e.g., in case the study investigator discovers a medical condition unrelated to study treatment, the participant may be referred to the local healthcare system). By receiving HZ/su OR Flu D-QIV in this study, the participants are likely to be protected against HZ or influenza, respectively.

2.3.3. Overall benefit/risk conclusion

Considering the measures taken to minimize risk to participants participating in this study, the potential or recognized risks identified in association with the study vaccines and study procedures are justified by the potential benefits that may be afforded to the participants receiving these vaccines and by the value of the information to be gained.

3. OBJECTIVES AND ENDPOINTS

Table 7 Study objectives and endpoints

Objectives	Endpoints*
Primary	
• To demonstrate the non-inferiority** of humoral immunogenicity of 2 doses of **HZ/su** when the first dose of HZ/su is co-administered with the mRNA-1273 booster dose compared to HZ/su administered alone.	• Anti-glycoprotein E (gE) antibody concentrations expressed as group geometric mean concentration (GMC) ratio at 1 month post-dose 2 of HZ/su (at Week 14 for HZ/suSeq, at Week 12 for HZ/suCoAd).
• To demonstrate non-inferiority** of humoral immunogenicity of 1 dose of **mRNA-1273 booster** when the first dose of HZ/su is co-administered with the mRNA-1273 booster dose compared to mRNA-1273 booster dose administered alone.	• Anti-S Protein antibody concentrations expressed as group GMC ratio§ at 1 month post mRNA-1273 booster dose (at Week 4 for HZ/suSeq and HZ/suCoAd).
• To demonstrate non-inferiority** of humoral immunogenicity of 1 dose of **Flu D-QIV** when co-administered with mRNA-1273 booster dose compared to Flu D-QIV administered alone based on geometric mean titer (GMT) of Flu D-QIV antibody titers against the 4 influenza strains.	• Anti-hemagglutinin inhibition (HI) antibody titers expressed as group GMT ratio against the 4 influenza strains included in Flu D-QIV at 1 month post Flu D-QIV (at Week 6 for FluD-QIVSeq, at Week 4 for FluD-QIVCoAd).
• To demonstrate non-inferiority** of humoral immunogenicity of 1 dose of **mRNA-1273 booster** when co-administered with Flu D-QIV compared to mRNA-1273 booster dose administered alone.	• Anti-S Protein antibody concentrations expressed as group GMC ratio§ at 1 month post mRNA-1273 booster dose (at Week 4 for FluD-QIVSeq and FluD-QIVCoAd).

Objectives	Endpoints*
Secondary	
• To demonstrate the non-inferiority** of humoral immunogenicity of 1 dose of **Flu D-QIV** vaccine when co-administered with mRNA-1273 booster dose compared to Flu D-QIV administered alone based on seroconversion rate (SCR) difference of Flu D-QIV HI antibody titers against 4 influenza strains.	• Anti-HI antibody SCR difference against the 4 influenza strains at 1 month post Flu D-QIV (at Week 6 for FluD-QIVSeq, at Week 4 for FluD-QIVCoAd).
• To characterize the anti-gE humoral immunogenicity at pre-vaccination and at 1 month post-dose 2 of HZ/su.	• Seropositivity rate with exact 95% CI at pre-vaccination (at Day 1 for HZ/suCoAd, at Week 2 for HZ/suSeq) and at 1 month post-dose 2 of HZ/su (at Week 14 for HZ/suSeq, at Week 12 for HZ/suCoAd). • Anti-gE antibody concentrations expressed as GMC with 95% CI at pre-vaccination (at Day 1 for HZ/suCoAd, at Week 2 for HZ/suSeq) and at 1 month post-dose 2 of HZ/su (at Week 14 for HZ/suSeq, at Week 12 for HZ/suCoAd). • Vaccine response rate (VRR) with exact 95% CIs at 1 month post-dose 2 of HZ/su (at Week 14 for HZ/suSeq, at Week 12 for HZ/suCoAd). • Mean geometric increase (MGI) from pre-vaccination with 95% CI at 1 month post-dose 2 of HZ/su (at Week 14 for HZ/suSeq, at Week 12 for HZ/suCoAd).
• To characterize the humoral immunogenicity of mRNA-1273 booster dose.	• Anti-S Protein antibody concentrations expressed as GMC§ with 95% CI at pre-vaccination (Day 1) and 1 month post mRNA-1273 booster dose (at Week 4 for all groups). • MGI§ from pre-vaccination with 95% CI at 1 month post mRNA-1273 booster dose (at Week 4 for all groups).
• To evaluate the humoral immunogenicity of Flu D-QIV. The assessment of SPR and SCR will be based on Center for Biologics Evaluation and Research's (CBER) criteria***.	• Anti-HI antibody titers against the 4 influenza strains included in Flu D-QIV expressed as GMTs with 95% CI at pre-vaccination and at 1 month post Flu D-QIV (at Week 6 for FluD-QIVSeq, at Week 4 for FluD-QIVCoAd). • Seroprotection rate (SPR) with exact 95% CI at pre-vaccination and at 1 month post Flu D-QIV (at Week 6 for FluD-QIVSeq, at Week 4 for FluD-QIVCoAd), overall and by age category (18-64 and ≥65 YOA). • Seropositivity rate with exact 95% CI at pre-vaccination and at 1 month post Flu D-QIV (at Week 6 for FluD-QIVSeq, at Week 4 for FluD-QIVCoAd). • MGI with 95% CI from pre-vaccination at 1 month post Flu D-QIV (at Week 6 for FluD-QIVSeq, at Week 4 for FluD-QIVCoAd). • SCR with exact 95% CI from pre-vaccination at 1 month post Flu D-QIV (at Week 6 for FluD-QIVSeq, at Week 4 for FluD-QIVCoAd), overall and by age category (18-64 and ≥65 YOA).

Objectives	Endpoints*
• To evaluate the safety and reactogenicity following administration of HZ/su, Flu D-QIV and mRNA-1273 booster dose, up to 30 days post-last vaccination and during the whole post-vaccination follow-up period.	• **Solicited adverse events (AEs):** Number and percentage of participants reporting each solicited local AE and each solicited systemic AE within 7 days (Days 1-7) after each dose and overall. • **Unsolicited AEs**: – Number and percentage of participants reporting unsolicited AEs within 14 days (Days 1-14) after each vaccination visit and overall after any vaccination visit for all groups. – Number and percentage of participants reporting unsolicited AEs within 30 days (Days 1-30) after each vaccination visit and overall after any vaccination visit for all groups. • **Serious adverse events (SAEs)**: – Number and percentage of participants reporting SAEs from first dose up to 30 days post-last dose within each group. – Number and percentage of participants reporting SAEs from first dose to study end. • **Potential immune mediated diseases (pIMDs) in HZ/su and mRNA-1273 booster cohort only:** – Number and percentage of participants reporting of pIMDs from first dose up to 30 days post-last dose within each group. – Number and percentage of participants reporting pIMDs from first dose to study end. • **Adverse events of special interest (AESIs):** – Number and percentage of participants reporting AESIs from first dose up to 30 days post-last dose within each group. – Number and percentage of participants reporting AESIs from first dose to study end. • **Suspected HZ episodes in HZ/su and mRNA-1273 booster cohort only:** Number and percentage of participants reporting clinically suspected HZ episodes from first dose to study end. • **COVID-19 cases**$^{\Delta}$: Number and percentage of participants meeting case definitions of COVID-19 from first dose to study end.
Exploratory	
• To evaluate the incidence of lab-confirmed HZ episodes following administration of HZ/su during the whole follow-up period.	• **Confirmed HZ cases in HZ/su and mRNA-1273 booster cohort only**: Number and percentage of participants with polymerase chain reaction (PCR) confirmed HZ episodes from first vaccination to study end.
• To characterize the anti-gE humoral immunogenicity at 1 month post-dose 1 of HZ/su.	• Seropositivity rate with exact 95% CI at 1 month post-dose 1 of HZ/su (at Week 6 for HZ/suSeq, at Week 4 for HZ/suCoAd).

Objectives	Endpoints*
	• Anti-gE antibody concentrations expressed as GMC with 95% CI at 1 month post-dose 1 of HZ/su (at Week 6 for HZ/suSeq, at Week 4 for HZ/suCoAd). • VRR with exact 95% CIs at 1 month post-dose 1 of HZ/su (at Week 6 for HZ/suSeq, at Week 4 for HZ/suCoAd). • Mean geometric increase (MGI) from pre-vaccination with 95% CI at 1 month post-dose 1 of HZ/su (at Week 6 for HZ/suSeq, at Week 4 for HZ/suCoAd).
• To further evaluate the immune response to the mRNA-1273 booster vaccine via neutralizing antibody titers in a sub-cohort of participants in all study groups.	• GMT with 95% CIs of SARS-CoV-2 neutralizing antibody titers in a sub-cohort of participants in each study group at pre-vaccination and at 1 month post mRNA-1273 booster dose (Week 4 for all groups).
• To evaluate further SARS-CoV-2/mRNA-1273 immune responses during the study.	• GMCs with 95% CI of anti-receptor binding domain (RBD) protein antibodies at pre-vaccination and 1 month post mRNA-1273 booster dose (at Week 4 for all groups). • Anti-nucleocapsid (N) protein seroconversion rate with exact 95% CI from pre-vaccination to 1 month post mRNA-1273 booster dose (at Week 4 for all groups).

§Pending final assay evaluations and validations prior to study specimen testing, this primary endpoint for all participants may be replaced with SARS-CoV-2 neutralizing antibody titers, and where applicable derived GMTs, GMT ratios, and MGI.
*The definitions and derivations of endpoint parameters are presented in Section 9.4.
**The success criteria for primary objectives and secondary objectives are presented in Section 9.1.
***CBER criteria are presented in Section 9.3.5.2.3
It should be noted that participants in the HZ/suSeq and FluD-QIVSeq groups will receive their HZ/su or Flu D-QIV, respectively, at Day 14 post mRNA booster vaccine dose at Day 1.
Δ Case Definitions in section 10.2.7

Details related to attributes of endpoint covering intercurrent events, population and treatment definition are provided in Section 9.

4. STUDY DESIGN

4.1. Overall design

This study is a Phase III, randomized, open-label, controlled, multicenter US-based study to evaluate the immune response and safety of both HZ/su in healthy adults 50 YOA and older and Flu D-QIV in healthy adults 18 YOA and older when administered sequentially or co-administered with mRNA-1273 booster vaccination.

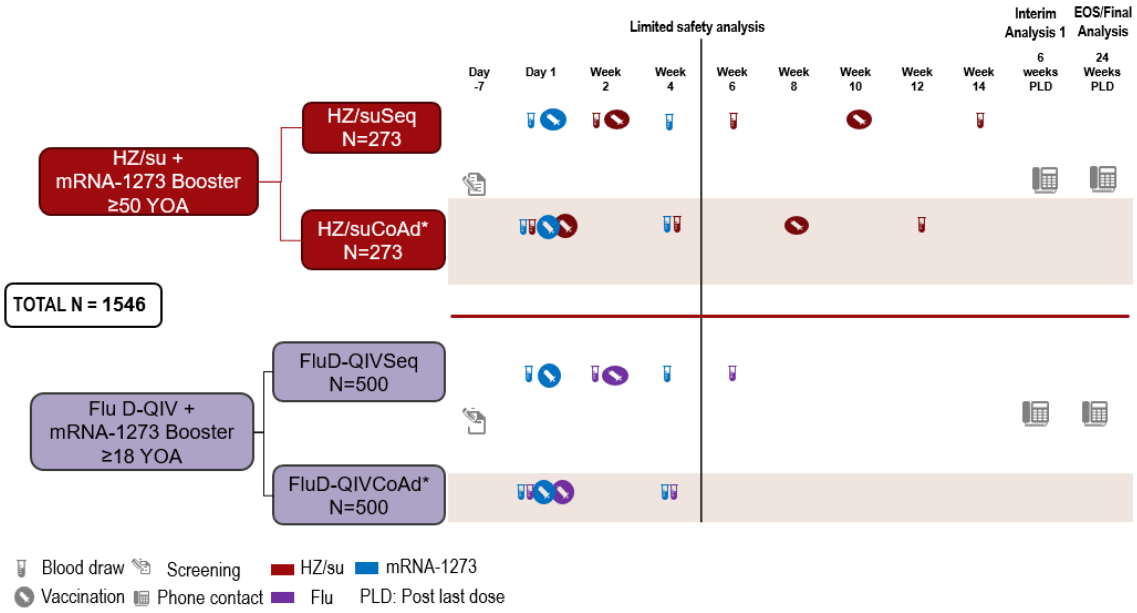
The study will be conducted in the U.S. and will enroll participants in 2 main study cohorts, HZ/su with mRNA-1273 booster vaccine administered sequentially or concomitantly and Flu D-QIV with mRNA-1273 booster vaccine administered sequentially or concomitantly, hereafter entitled HZ/su and mRNA-1273 booster cohort and Flu D-QIV and mRNA-1273 booster cohort, respectively (Figure 1).

Potential participants will be triaged initially to either study cohort (HZ/su and mRNA-1273 booster, Flu D-QIV and mRNA-1273 booster) based upon criteria such as seasonal influenza vaccine availability, known eligibility criteria (such as age and vaccination history), and current study enrollment status. Subsequently, enrolled (i.e., having signed an informed consent form) and eligible participants in each cohort will be randomized in a 1:1 ratio to each of the 2 study groups within each cohort (Table 8). Staggered randomization will be implemented at the beginning of the study for safety monitoring (see Section 8.2.2.1).

- In the HZ/su and mRNA-1273 booster cohort, 546 participants will be randomized in a 1:1 ratio so that 273 participants are assigned to each study group. The first group (**HZ/suSeq group**) will receive the mRNA-1273 booster dose followed approximately 2 weeks later by the first dose of HZ/su, while the second group (**HZ/suCoAd group**) will receive the mRNA-1273 booster dose co-administered with the first dose of HZ/su. All participants in the HZ/suSeq group and the HZ/suCoAd group will receive the second dose of HZ/su approximately 2 months after the first HZ/su dose. Randomization into each group will be stratified by age (50 to 59, 60 to 69, and ≥ 70 YOA) and will be set to ensure a minimum number of 138 participants are assigned to the ≥ 70 YOA stratum, 69 participants to each group.
- In the Flu D-QIV and mRNA-1273 booster cohort, 1000 participants will be randomized in a 1:1 ratio so that 500 participants are assigned to each study group. The first group (**FluD-QIVSeq group**) will receive the mRNA-1273 booster dose followed approximately 2 weeks later by the Flu D-QIV dose, while the second group (**FluD-QIVCoAd group**) will receive the mRNA-1273 booster dose co-administered with the Flu D-QIV dose. Randomization into each group will be stratified by age (18 to 64 and ≥ 65 YOA) and will be set to ***target (Amended 21 September 2021)*** a minimum number of 150 participants are assigned to the ≥ 65 YOA stratum, 75 participants to each group.

All study participants will be followed for safety until 6 months post the last dose of the study vaccine with the total duration of study participation approximately 34 and 26 weeks in the HZ/su and mRNA-1273 booster cohort and Flu D-QIV and mRNA-1273 booster cohort, respectively.

Figure 1 Study design overview



EOS = end of study, telephone contact at 24 weeks post last vaccine dose; N = number of participants enrolled and randomized; PLD = post last dose
*Safety Review Team evaluation of 7 days post-dosing after Visit 1 safety data for initial 10% vaccinated in the HZ/suCoAd group and 5% vaccinated in the FluD-QIVCoAd group prior to full randomization in the respective cohorts ***(Amended 21 September 2021)***

Table 8 Study groups, intervention, and blinding

Cohort	Study Groups	Number of Randomized Participants	Age	Study Interventions	Blinding
					Visit 1 → Phone Contact 2 (Open-label)*
HZ/su and mRNA1273 Booster	HZ/suSeq	273	≥50 years**	mRNA-1273 booster HZ/su	x
	HZ/suCoAd	273			
Flu D-QIV and mRNA-1273 Booster	FluD-QIVSeq	500	≥18 years**	mRNA-1273 booster Flu D-QIV	x
	FluD-QIVCoAd	500			

*This is an open-label study; however, the specific participant vaccination schedule (sequential or coadministration) will be randomly assigned within each cohort.
** Randomization will be set to ensure at least 69 participants per group will be ≥ 70 YOA in the HZ/su and mRNA-1273 booster cohort and ***to target*** at least 75 participants ≥ 65 YOA ***per group*** in the Flu D-QIV and mRNA-1273 booster cohort. ***(Amended 21 September 2021)***

4.2. Scientific rationale for study design

The study was designed after careful considerations of the current healthcare needs and expectations related to vaccinations of the adult population in the U.S.

The U.S Centers for Disease Control and Prevention (CDC) recommends receipt of *Shingrix* to everyone 50 YOA and older, to prevent shingles and its complications [CDC, 2019].

According to CDC, everyone 6 months of age and older should receive a seasonal influenza vaccine every season with rare exceptions. For 2021-2022, CDC recommends use of any licensed, influenza vaccine that is appropriate for the recipient's age and health status, including inactivated influenza vaccine, recombinant influenza vaccine, or live attenuated nasal spray influenza vaccine [CDC, 2021a].

As of summer, 2021, vaccines against COVID-19 in people ages 12 years and older have become an essential part of healthcare procedures to control the COVID-19 pandemic. ***With the emergence and spread of the SARS-CoV-2 virus variants that may not be sufficiently controlled by the primary vaccinations,*** **periodic** administration of booster COVID-19 vaccines after primary vaccination ***is either already recommended for specific populations or is under consideration by various health agencies***. ***(Amended 21 September 2021)***

Current CDC guidance on the coadministration of COVID-19 vaccines with other routine vaccinations is as follows: "COVID-19 vaccines and other vaccines may now be administered without regard to timing. This includes simultaneous administration of COVID-19 vaccine and other vaccines on the same day, as well as coadministration within 14 days. It is unknown whether reactogenicity of COVID-19 vaccine is increased with coadministration, including with other vaccines known to be more reactogenic, such as adjuvanted vaccines or live vaccines" [CDC, 2021c].

The current study is designed to provide reactogenicity, safety, and immunogenicity data for when a seasonal influenza virus vaccine or an adjuvanted Herpes Zoster subunit vaccine is administered at the same time or two weeks following a potential COVID-19 mRNA booster vaccine. This is important needed data expected to help public health authorities provide more evidence-based guidance and health care providers to make decisions on such vaccine coadministrations.

4.2.1. Rationale for randomization

This will be an open-label study. Comparative analyses between the 2 study groups will only be conducted within each study cohort; therefore, once participants have been triaged to their study cohort, to prevent any selection bias in assignment to each study group, they will be randomly assigned to either the co-administration or sequential study group. Consequently, neither study staff nor participants will be aware which group the participant will be assigned to prior to the randomization.

4.3. Justification for dose

Fluarix Quadrivalent and *Shingrix* are vaccines licensed by the FDA for use in the U.S and shall be administered in this study as per their approved doses and schedule.

Moderna's mRNA-1273 vaccine is authorized for use in the U.S in adults 18 YOA and older under an EUA by the FDA and as a primary series of two 100 µg doses administered 1 month apart. Doses of 100 µg and 50 µg of the same vaccine are being investigated as a potential booster dose to be administered following the primary series. Preliminary results have shown that a 50 µg mRNA-1273 booster dose at least 6 months following the primary series substantially increases neutralizing antibodies against the wildtype SARS-CoV-2 virus and other tested variants, with a safety profile consistent

with the known profile in earlier clinical trials [Wu, 2021b]. Currently, in light of the evolving emergence of SARS-CoV-2 variants, it is anticipated that a booster vaccine ***may be*** needed. ***The current available data suggests that 50 µg (half dose)*** of mRNA-1273 may be ***sufficient to boost immune response against the existing variants. This half dose is now recommended for boosting in the UK for certain populations at high risk for severe disease, to be administered 6 months post the primary series. This dose is also under review by other health agencies***. As a result, ***50*** µg of mRNA-1273 will be used in this study.

To note: If a different dose of mRNA-1273 is approved and recommended for use as a booster in the US while the study is ongoing, the dose of mRNA-1273 booster in the study will be adjusted in the HZ/su and mRNA-1273 booster cohort to the approved dose. The sample size in this cohort will also be adjusted accordingly to ensure sufficient power to achieve the corresponding primary objectives with the adjusted dose. The data generated with the 50 µg of mRNA-1273 booster will then be informative and add to the body of safety and immunogenicity data at this dose level. (Amended 21 September 2021)

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 as described in the protocol.

The End of Study is defined as the date of the Last Participant Last Visit (LPLV, also may appear as last subject last visit, LSLV) or date of last testing results released of the Human Biological Samples related to primary and secondary endpoints, whichever comes last. End of Study must be achieved no later than 8 months after the LPLV.

5. STUDY POPULATION

Adherence to the inclusion and exclusion criteria specified in the protocol is essential. Deviations from these criteria are not allowed because they can jeopardize the scientific integrity, regulatory acceptability of the study, or safety of the participant.

5.1. Inclusion criteria

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

- Participants who in the opinion of the investigator, can and who will comply with the requirements of the protocol (e.g., completion of the eDiaries, return for follow-up visits).
- Written informed consent obtained from the participant prior to performance of any study-specific procedure.
- Age at study entry:
  - ***For HZ/su and mRNA-1273 booster cohort***: A male or female aged 50 years or older at the time of randomization.
  - ***For Flu D-QIV and mRNA-1273 booster cohort***: A male or female aged 18 years or older at the time of enrollment.

- Healthy participants or medically stable patients as established by medical history and clinical examination at screening. A stable medical condition is defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 3 months before enrolment.
- Participants who have a documented previous mRNA-1273 primary vaccination series completed (i.e., both doses) at least 6 months prior to first vaccination.
- Female participants of non-childbearing potential (see definition in Section 10.3) may be enrolled in the study. Non-childbearing potential is defined as pre-menarche, current bilateral tubal ligation or occlusion, documented total hysterectomy, bilateral ovariectomy, or bilateral salpingectomy, or post-menopause. Refer to Section 10.3.1 for definitions of women of childbearing potential (WOCBP), menarche and menopause.
- Female participants of childbearing potential may be enrolled in the study, if the participant:
  - Has practiced effective contraception (see definition in Section 10.3) for 1 month prior to study intervention administration, and
  - Has a negative pregnancy test on the day of study intervention administration, and
  - Has agreed to continue effective contraception during the study until 2 months after completion of the study vaccination series.

  Refer to Section 10.3.1 for definition of WOCBP and adequate contraception.

5.2. Exclusion criteria

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

5.2.1. Medical conditions

- Any clinical condition that, in the opinion of the investigator, might pose additional risk to the participant due to participation in the study or might confound post-study intervention administration safety assessments (e.g., tattoos overlying either study intervention administration site).
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the study interventions, including a known history of severe allergic reaction (e.g., anaphylaxis) to any component of any of the study vaccines.
- Any history of Guillain-Barré syndrome.
- Any history of myocarditis or pericarditis.
- Acute or chronic clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by medical history or physical examination.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- Hypersensitivity to latex.
- For HZ/su and mRNA-1273 booster cohort: history of Herpes Zoster.

5.2.2. Prior/concomitant therapy

- Use of any investigational or non-registered product (drug, vaccine or medical device) other than the study intervention(s) during the period beginning 30 days before the first dose of study intervention(s) (Day -29 to Day 1), or their planned use during the study period.
- Planned administration/administration of a vaccine not foreseen by the study protocol in the period starting 30 days before first dose and ending 30 days after the last dose of study intervention administration. However, ***for HZ/su and mRNA-1273 booster cohort:*** licensed pneumococcal vaccines and non-replicating vaccines (i.e., inactivated and subunit vaccines, including inactivated and subunit influenza vaccines, with or without adjuvant for seasonal or pandemic flu) may be administered up until 8 days prior to dose 1 of HZ/su and/or dose 2 of HZ/su and/or at least 14 days after any dose of HZ/su. ***For Flu D-QIV and mRNA-1273 booster cohort:*** licensed pneumococcal vaccines and non-replicating vaccines (i.e., inactivated and subunit vaccines, other than influenza vaccines) may be administered up until 8 days prior to dose 1 of Flu D-QIV and/or at least 30 days after any dose of Flu D-QIV. For time interval between other routine vaccines with mRNA-1273 booster dose (administered in the study), local guidelines must be followed.

  In case emergency mass vaccination for an unforeseen public health threat (e.g., a pandemic) is organized by public health authorities outside the routine immunization program, the time period described above can be reduced if necessary for that mass vaccination vaccine, provided this vaccine is licensed and used according to its Product Information.
- Administration of long-acting immune-modifying drugs at any time during the study period (e.g., infliximab).
- Administration of immunoglobulins and/or any blood products or plasma derivatives during the period starting 3 months before the first dose of study intervention(s) up to 1 month post-last dose or planned administration during the study period.
- Prior planned or 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. For corticosteroids, this will mean more than 14 days in total of prednisone ≥20 mg/day or equivalent is not allowed. Inhaled, intra-articular and topical steroids are allowed.
- ***For HZ/su and mRNA-1273 booster cohort:*** Previous vaccination against Herpes Zoster with the exception of receipt of live attenuated HZ vaccine.
- ***For Flu D-QIV and mRNA-1273 booster cohort*****:** Administration of a seasonal influenza vaccine during the 6 months preceding entry into the study.
- Prior administration of an investigational or licensed coronavirus (SARS-CoV, MERS-CoV, SARS-CoV-2) vaccine **except for mRNA-1273 vaccine.**
- Any contraindication to the study intervention(s).

5.2.3. Prior/concurrent clinical study experience

- Planning to or concurrently participating in another clinical study (including current / planned simultaneous participation in another interventional study to prevent or treat COVID-19), 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) (see the definitions in the Glossary of terms).

5.2.4. Other exclusions

- Pregnant or lactating female.
- Female planning to become pregnant or planning to discontinue contraceptive precautions within 2 months following last study vaccination.
- Indications of drug abuse or excess alcohol use as deemed by investigator to potentially confound safety assessments or render participant unable or unlikely to adhere to protocol requirements.

Refer to Section 5.5 for criteria for temporary delay of enrollment and/or interventions.

5.3. Lifestyle considerations

Not applicable.

5.4. Screening failures

Screen failures are defined as participants who consented to participate in the clinical study but were not subsequently randomized. Screen failures will be listed in the source data and entered in the eCRF.

A participant who failed screening or was unable to complete screening during the allowed window can be re-screened later at the discretion of the investigator and following GSK approval.

5.5. Criteria for temporarily delaying randomization and/or study intervention administration

Randomization/study intervention administration may be postponed within the permitted time interval until transient conditions cited below are resolved and the participant stays eligible:

- Acute disease and/or fever at the time of randomization and/or study intervention administration. Fever is defined as temperature ≥ 38.0°C (100.4°F) by any route. The preferred location for measuring temperature will be oral route.
- Participants with a minor illness without fever may be enrolled and/or dosed at the discretion of the investigator.
- Use of antipyretics and/or analgesics and/or antibiotics within 3 days prior to study intervention administration.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

Refer to the Glossary of terms for the definition of study intervention.

6.1. Study interventions administered

Table 9 Study interventions administered *(Amended 21 September 2021)*

Study Intervention Name:	**HZ/su**		**Flu D-QIV**	**mRNA-1273**
Product Name:	VZV gE	$AS01_B$	Flu D-QIV 2021-2022 NH	COVID-19 mRNA Vaccine
Study intervention Formulation:	VZV gE (50 µg)	$AS01_B$: QS-21 (50 µg), MPL (50 µg), liposomes; water for injections *q.s.* 0.5 mL	Flu Quadrivalent Influenza vaccine 15 µg per strain*/dose	100 µg per dose (embedded in SM-102 lipid nanoparticles); water for injections *q.s.* 0.5 mL
Formulation Dose Form:	Powder for suspension for injection	Suspension for injection	Suspension for injection	Dispersion for injection
Presentation:	Vial	Vial	Syringe	Vial
Product Category:	Biologic		Combination product	Biologic
Type:	Study Vaccine		Study Vaccine	Study Vaccine
Route of Administration:	Intramuscular injection		Intramuscular injection	Intramuscular injection
Administration Site:	Left deltoid		Left deltoid	Right deltoid
Number of Doses to be Administered:	2		1	1
Volume to be Administered:**	0.5 mL		0.5 mL	***0.25*** mL
Packaging and labeling:	Refer to the Pharmacy Manual			
Manufacturer:	GSK		GSK	Moderna

HZ/su = herpes zoster subunit vaccine; VZV = varicella zoster virus; gE = glycoprotein E; AS01B = adjuvant system 01B; NH = North hemisphere; QS-21 = Quillaja saponaria Molina, fraction 21 (Licensed by GSK from Antigenics Inc, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation); MPL = 3-O-desacyl-4'-monophosphoryl lipid A; *q.s.* = *quantum satis*

* A/Victoria/2570/2019 (H1N1), IVR-215 (15 µg HA); A/Tasmania/503/2020 (H3N2), IVR-221 (15 µg HA); B/Washington/02/2019 (15 µg HA); B/Phuket/3073/2013 (15 µg HA); Water for injections *q.s.* 0.5 mL

Refer to the Pharmacy Manual for ***more details*

Study participants must be observed closely for at least 30 minutes after the administration of the study interventions. The duration of the observation period can be extended at the investigator's discretion. Appropriate medical treatment must be readily available during the observation period in case of significant hypersensitivity reactions, anaphylaxis, or syncope.

6.2. Preparation, handling, storage, and accountability

The study interventions must be stored in a secured place within the temperature range specified on the study intervention's label. The storage temperature should be continuously monitored and recorded with a calibrated (if not validated) temperature monitoring device(s).

Only authorized study personnel should be allowed access to the study interventions. Storage conditions will be assessed by a PPD study contact during pre-study activities. Refer to the Pharmacy Manual for more details on storage and handling of the study interventions.

6.3. Measures to minimize bias: randomization and blinding

6.3.1. Participant identification

At enrollment, participant identification numbers (IDs, may also be referred to as Subject Number) will be assigned sequentially to the participants who consented to participate in the study according to the range of participant IDs allocated to each study center. The IDs will be assigned upon site's completion of the screening form in Interactive Web Response System through Interactive Response Tool (IRT).

6.3.2. Randomization to study intervention

Within each cohort, participants will be centrally randomized to 1 of the 2 study groups (sequential or co-administration) and receive a Randomization Number through IRT. At randomization, the IRT system will validate the participant's age. Participants in the HZ/su and mRNA-1273 booster cohort will be stratified by age group (50 to 59 YOA, 60 to 69 YOA, and ≥ 70 YOA) prior to randomization. Participants in the Flu D-QIV and mRNA-1273 booster cohort will also be stratified by age group (18 to 64 YOA and ≥ 65 YOA) prior to randomization.

The target will be to randomize approximately 546 eligible participants in the HZ/su and mRNA-1273 booster cohort, who would be randomly assigned to one of two study groups in a (1:1) ratio (approximately 273 participants in each group). The stratification by age will be set to ensure a minimum of 69 participants in the ≥ 70 YOA stratum in each group.

The target will be to randomize approximately 1000 eligible participants in the Flu D-QIV and mRNA-1273 booster cohort, who would be randomly assigned to 1 of 2 study groups in a (1:1) ratio (approximately 500 participants in each group). The stratification by age will be set to target a minimum of 75 participants in the ≥ 65 YOA stratum in each group.

6.3.3. Intervention allocation to the participant

Intervention (may be referred to as a treatment number or an intervention kit number) allocation for each participant will be performed through IRT at the first intervention visit. Once a participant ID is allocated, IRT will determine the study group and will provide the treatment number (kit number). The treatment number allocated to the participant will be recorded in IRT and treatment number actually administered will be recorded in the eCRF. As mRNA-1273 is presented in a multidose vial, the treatment number for a subsequent dose of mRNA-1273 to be administered to a different participant from the same vial, will be recorded in a custom table with the dose appended (e.g., treatment number/01, treatment number/02, treatment number/03, etc.).

6.3.4. Blinding and unblinding

Not applicable as this is an open-label study. Neither the participant nor the investigator can choose which group the participant will be allocated to. Once randomization has been completed, all involved parties will be aware of the participant's group allocation.

Codes will be used to link the participant and study to each sample to be tested in the laboratory. There will be no link between the study intervention groups and the identity of the participant.

6.3.4.1. Emergency unblinding

This is an open-label trial. Therefore, this section is not applicable.

6.4. Study intervention compliance

Participants will receive study intervention from the authorized study center staff. The date and site of administration of each study intervention dose in the clinic will be recorded in the source documents and in the eCRF.

6.5. Dose modification

Section is not applicable.

6.6. Continued access to study intervention after the end of the study

There will be no continuing access to the study intervention after the end of the study.

6.7. Treatment of overdose

Any dose of any study vaccine greater than the one required per protocol is considered an overdose. All cases of vaccine overdose should be reported as protocol deviations. Any signs or symptoms resulting from an overdose should be reported as AEs, or SAEs if SAE criteria are met; overdose per se should not be reported as an AE/SAE. GSK does not recommend specific treatment for an overdose; however, any resulting adverse reaction should be treated symptomatically.

6.8. Concomitant therapy

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

The following concomitant medication/product/vaccines must be recorded in the eCRF:

- All concomitant medications ongoing at screening and any new concomitant medications administered after the first dose of study intervention until the end of the last unsolicited AE collection period.
- All concomitant medication associated with an AE, including vaccines/products, administered after the first dose of study intervention.
- All concomitant medication leading to discontinuation of the study intervention or elimination from the analysis (e.g., immunosuppressive or immune-modifying medications), including products/vaccines.
- All concomitant medication which may explain/cause/be used to treat an SAE/AESI/pIMD including vaccines/products, as defined in Sections 8.3.1 and 10.2.10. These must also be recorded in the Expedited Adverse Event report.

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

The record of a concomitant therapy should include at a minimum the reason for use, dates of administration including start and end dates, dosage information including dose and frequency.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of study intervention

'Discontinuation' of study intervention refers to any participant who has not received all planned doses of study intervention. A participant who discontinued study intervention may continue other study procedures (e.g. safety or immunogenicity), planned in the study protocol at the discretion of the investigator.

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

- AE requiring expedited reporting to PPD (see Section 10.2.12).
- Unsolicited non-serious AE (see Section 10.2.4).
- Solicited AE (see Section 10.2.3).
- Not willing to be administered the study intervention.
- Other (specify).

7.1.1. Contraindications to subsequent study intervention administration

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

Participants who no longer meet any applicable eligibility criteria or meet any of the criteria listed below should not receive additional doses of study intervention. Such participants should be encouraged to continue other study procedures, at the investigator's discretion (Section 10.2.10.1). All relevant criteria for discontinuation of study intervention administration must be recorded in the eCRF.

- Participants who experience any SAE judged to be possibly or probably related to study intervention or non-study concomitant vaccine/product, including hypersensitivity reactions.
- Participants who develop any new condition which, in the opinion of the investigator, may pose additional risk to the participant if he/she continues to participate in the study.
- Any condition that in the judgment of the investigator would make intramuscular injection unsafe.
- Participants who develop any new condition that may impair their ability to adhere to required study procedures.
- Occurrence of a new pIMD or the exacerbation of an existing pIMD that in the opinion of the investigator, exposes the participant to unacceptable risk from subsequent vaccination. In such cases, the investigator should use his/her clinical judgement prior to administering the next dose of the study intervention. Refer to Section 10.2.5 for the definition of pIMD.
- Occurrence of a new AESI or the exacerbation of an existing AESI that in the opinion of the investigator, exposes the participant to unacceptable risk from subsequent doses of study intervention. Refer to Section 10.2.6 for the definition of AESI.
- Pregnancy.

7.2. Participant discontinuation/withdrawal from the study

A participant is considered to have withdrawn from the study if no new study procedure has been performed or no new information has been collected for him/her since the date of withdrawal/last contact.

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

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

All data and samples collected up to and including the date of withdrawal of/last contact with the participant will be included in the study analyses.

The investigator will document whether the decision to withdraw a participant from the study was made by the participant himself/herself or by the investigator. The primary reason for study withdrawal will be documented in the eCRF, based on the list below:

- AEs requiring expedited reporting to PPD (see Section 10.2.12).
- Unsolicited non-serious AEs (see Section 10.2.4).
- Solicited AE (see Section 10.2.3).
- Withdrawal by participant, not due to an AE*.
- Migrated/Moved from the study area.
- Lost to follow-up (see Section 7.3).
- Sponsor study termination.
- Other (specify).

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

Participants who are withdrawn from the study because of AEs/SAEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigator will follow participants who are withdrawn from the study due to an AE/SAE until the event is resolved or as described in Section 10.2.10.2.

7.3. Lost to follow-up

A participant will be considered ‘lost to follow-up’ if he/she fails to return for scheduled visits and cannot be contacted by the study site.

The following actions, unless specified differently in other study-related materials, must be taken if a participant fails to return to the clinic for a required study visit:

- The study center must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant’s last known mailing address or local equivalent methods). These contact attempts should be documented.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

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

8. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are only permitted when necessary for the management of immediate safety concerns for the participant.

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

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

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

The investigator will maintain a 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 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 study plans provide the investigator and site personnel with detailed administrative and technical information that does not impact participant safety.

8.1. Immunogenicity assessments

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

Findings in this or future studies may make it desirable to use samples acquired in this study for research not planned in this protocol. In this case, all participants in countries where this is allowed will be asked to give consent to allow GSK or a contracted partner, to use the samples for further research. The further research will be subject to prior IRB (or independent ethics committee) approval, if required by local legislation.

Information on further research and its rationale can be obtained from GSK.

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

By default, collected samples will be stored for a maximum of 20 years. This storage period begins when the last participant performs the last study visit. This timeline can be adapted based on local laws, regulations or guidelines requiring different timeframes or procedures. In all cases, the storage period should be aligned with participant's consent. These additional requirements must be formally communicated to, discussed and agreed with GSK.

8.1.1. Biological samples

Refer to Table 10 for the schedule and details of sampling activities during this study.

8.1.2. Laboratory assays

Table 10 Laboratory assays

Assay Type	System	Component	Method	Laboratory
Humoral Immunity (Antibody Determination)	Serum	Anti-glycoprotein E Ab.IgG	ELISA	GSK
		Anti-S Protein Ab*	Multiplex Electrochemiluminescence assay**	PPD
		SARS-CoV-2 NA	Neutralization assay***	Nexelis
		A/Victoria/2570/2019	Hemagglutination Inhibition	Q2
		A/Tasmania/503/2020		Q2
		B/Washington/02/2019		Q2
		B/Phuket/3073/2013		Q2

Ab = antibody; ELISA = enzyme linked immunosorbent assay; NA = neutralizing antibody
*Responses to other antigens (e.g., anti-N and anti-RBD proteins) may be generated in addition to anti-S Protein.
**Other serological assays may be used to measure antibody responses
***Assay to be conducted on the virus strain in the booster dose

Table 11 Molecular biology

System	Component	Method	Unit	Laboratory
HZ lesion sample	Varicella Zoster Virus DNA	PCR	No unit	GSK
	Actin Gene DNA	PCR	No unit	GSK

HZ = herpes zoster; DNA = deoxyribonucleic acid; PCR = polymerase chain reaction

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

Exploratory testing on the vaccines and/or on the disease under study may be performed within the framework of the study (i.e., exploratory objective) if deemed necessary for accurate interpretation of the data. These assays may or may not be represented in the objectives/endpoints of the study protocol. Pending final assay evaluations and validations prior to study sample testing, the multiplex electrochemiluminescence testing for assessing mRNA-1273 booster immune responses as the primary endpoint may be replaced with a neutralization assay to measure SARS-CoV-2 neutralizing antibody titers in all study participants, and if not, the assessment of neutralizing antibody titers will be restricted to a sub-cohort of approximately 50 participants. In addition, the exploratory assessment of anti-gE humoral immunogenicity at 1 month post-dose 1 of HZ/su may be limited, based upon the nature of the responses observed following the second dose of HZ/su and scientific relevance.

GSK/ contract research organization's (CRO) clinical laboratories have established a Quality System supported by procedures. The activities of GSK's/ CRO's 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 12 Immunological read-outs

Study Group	Number of participants	Visit 1 Day 1	Visit 2	Visit 3	Visit 4	Visit 6
HZ/suSeq	273	SARS-CoV-2 Neutralizing Ab* Anti-S Protein IgG Ab**	Anti-gE Ab	SARS-CoV-2 Neutralizing Ab* Anti S Protein IgG Ab**	Anti-gE Ab	Anti-gE Ab
HZ/suCoAd	273	SARS-CoV-2 Neutralizing Ab* Anti-S Protein IgG Ab** Anti-gE Ab	SARS-CoV-2 Neutralizing Ab * Anti S Protein IgG Ab** Anti-gE Ab	-	Anti-gE Ab	-
FluD-QIVSeq	500	SARS-CoV-2 Neutralizing Ab* Anti-S Protein IgG Ab**	HI Ab	SARS-CoV-2 Neutralizing Ab* Anti S Protein IgG Ab**	HI Ab	-
FluD-QIVCoAd	500	SARS-CoV-2 Neutralizing Ab* Anti-S Protein IgG Ab** HI Ab	SARS-CoV-2 Neutralizing Ab* Anti S Protein IgG Ab** HI Ab	-	-	-

Ab = antibodies; IgG = immunoglobulin G
*Samples may be tested on a sub-cohort (approximately 50 evaluable participants) post-hoc, based on other observed immune assay results or in all study participants if selected as a primary endpoint
**Responses to other antigens (e.g., anti-N and anti-RBD proteins) may be generated in addition to anti-Spike Protein

8.1.4. Immunological correlates of protection

No immunological correlate of protection against HZ or COVID-19 have yet been identified (see current IBs for *Shingrix* and mRNA-1273) (see the Glossary of terms for the definition of immunological correlate).

Although no generally accepted immunological correlate of protection has been demonstrated so far against influenza (either seasonal or pandemic) with respect to specific levels of HI-specific antibody titer post-vaccination induced with inactivated influenza virus vaccines, the protective role of antibodies against haemagglutinin and, to a lesser extent, neuraminidase, is well established and has been demonstrated both in experimentally infected animals and humans [Brydak, 2000; 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. Reciprocal HI antibody titers of 40 or greater have been associated with protection from influenza illness in at least 50% of adult subjects in some human challenge studies [Hannoun, 2004; Hobson, 1972].

8.2. Safety assessments

The investigator and his/her designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE. The investigator and designees are responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant's withdrawal from the study intervention or study.

Further details are provided in Section 10.2.

8.2.1. Pre-intervention administration procedures

8.2.1.1. Collection of demographic data

Demographic data such as date of birth (year only), age, sex, race, and ethnicity will be collected from each participant and recorded.

8.2.1.2. Medical/Vaccination history

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

Medical history should be collected, recorded, and verified that all inclusion and none of the exclusion criteria related to medical and vaccination history (Section 5.2) are met.

Both axillae will be examined for lymph nodes (swelling/tenderness) and unless exclusionary, if present, will be documented as medical history. Skin overlying both deltoid muscles for evidence of any findings that may confound local solicited AE assessments (e.g., rashes or tattoos) will be assessed, and if present, the participant will be excluded.

8.2.1.3. History-directed physical examination

History-directed physical examination will be performed. If the investigator determines that the participant's health on the day of the study intervention administration temporarily precludes dosing, the visit will be rescheduled (see Section 5.5).

8.2.1.4. Pregnancy test

Female participants of childbearing potential must perform a urine pregnancy test on the day of and before the administration of any dose of study intervention. Pregnancy testing must be done even if the participant is menstruating at the time of the study visit. The study intervention may only be administered if the pregnancy test is negative. If a prior serum test result is necessary as per IRB requirement, unless the sample is obtained on the day of study intervention, then a urine test must also be performed on the day of and prior to study intervention administration.

The urine pregnancy test kits (human chorionic gonadotropin [hCG] hormone test strip) provided to the study sites are approved by the FDA. Serum pregnancy testing, if required, will be performed as per standard of care.

Refer to Section 10.3.3.1 for the information on study continuation for participants who become pregnant during the study.

8.2.1.5. Warnings and precautions to administration of study intervention

Warnings and precautions to administration of study intervention must be checked at each visit with planned administration of study intervention. Refer to the approved product label/package insert for *Shingrix* and *Fluarix Quadrivalent*.

8.2.2. Study holding rules and safety monitoring

8.2.2.1. Safety review team oversight and staggered randomization

An internal GSK safety review team (SRT) which may also include staff from Moderna, will oversee the safety of this study. Randomization will be temporarily paused after 10% and 5% of participants in the HZ/su and mRNA booster cohort and Flu D-QIV and mRNA booster cohort, respectively, have received the study vaccinations at Visit 1 and been followed up for 7-days post-vaccination. Safety data for 7 days post-dosing will be reviewed for the HZ/suCoAd and FluD-QIVCoAd groups by the SRT at this pre-specified scheduled review. Randomization shall also be temporarily put on hold and an *ad hoc* SRT review will be performed if any of the holding rule criteria are met at any time during the study. Randomization can only be resumed following SRT approval to do so in the pre-specified scheduled or *ad hoc* SRT review.

The SRT will also perform safety reviews after all participants in the HZ/su and mRNA-1273 booster cohort sequential group have completed 14 days of follow-up after their HZ/su dose 1, and when all participants in the Flu D-QIV and mRNA-1273 cohort sequential group have completed 14 days of follow-up after their Flu D-QIV dose.

The SRT will also review all the safety data including solicited AEs, unsolicited AEs, SAEs, AESIs, IMCs, pIMDs, COVID-19 cases, pregnancies and suspected HZ cases at regular intervals during the conduct of the study while monitoring the safety holding rules (Section 8.2.2).

Any potential safety concern related to conduct of the study will be managed as per internal GSK process.

8.2.2.2. Study holding rules

Study holding rules are defined in Table 13. These holding rules are applicable only for the co-administration groups (HZ/suCoAd and FluD-QIVCoAd). If any study team member from a site, PPD, or GSK identifies that a holding rule criterion may have been met, they must inform the PPD MM immediately (by calling the 24 hours safety hotline number; see section 8.3.3.1), who will notify the SRT, and if confirmed, PPD will place study randomization on hold until the SRT has been able to review all applicable safety data and provided a decision on whether to continue with randomizations and the study as planned or otherwise. Moreover, if the investigator becomes aware of a holding rule (*e.g.*, 1a or 1d) being met, he/she must suspend administration of the study intervention and inform the PPD MM immediately. Further details of SRT processes are provided in the SRT Charter.

Table 13 Study holding rules

Holding Rule	Event	Number or Percentage of Participants	
		For HZ/suCoAd group	For FluD-QIVCoAd group
1a	Death or any life-threatening SAE that can be reasonably attributed to the vaccination	1 participant	1 participant
1b	Any non-life-threatening SAE that can be reasonably attributed to the vaccination	3/28 participants (for initial SRT review); For the rest of the study: 10%	3/25 participants (for initial SRT review); For the rest of the study: 10%
1c	Any withdrawal from the study (by investigator or participant request) following a Grade 3 AE that can be reasonably attributed to the vaccination	3/28 participants (for initial SRT review); For the rest of the study: 10%	3/25 participants (for initial SRT review); For the rest of the study: 10%
1d	Fever >40°C (104°F), OR Any solicited local event or solicited systemic AE leading to hospitalization, each within the 7-day (Days 1-7) post-vaccination period	2 participants	2 participants
2a	Any Grade 3 solicited systemic AE (lasting 48h or more) within the 7-day (Day 1-7) post-vaccination period	6/28 participants (for initial SRT review); For the rest of the study: 20%	5/25 participants (for initial SRT review); For the rest of the study: 20%
2b	Any Grade 3 unsolicited AE, that can be reasonably attributed to the vaccination, within the 7-day (Day 1-7) post-vaccination period	3/28 participants (for initial SRT review); For the rest of the study: 10%	3/25 participants (for initial SRT review); For the rest of the study: 10%

Risk assessment for study holding rules

Figure 2 illustrates that, with 28 participants per study group in the HZ/su and mRNA-1273 booster vaccine cohort at the pre-specified scheduled SRT review:

- Each holding rule 1a and 1d has more than 75% chance of not being met for vaccination with a true incidence rate of 1% and has more than 95% chance of being met for vaccination with a true incidence rate above 10%.
- Each holding rule 1b, 1c and 2b has more than 54% chance of not being met for vaccination with a true incidence rate below 10% and more than 81% chance of being met for vaccination with a true incidence rate above 15%.
- Each holding rule 2a has more than 76% chance of not being met for vaccination with a true incidence rate below 15% and more than 50% chance of being met for vaccination with a true incidence rate above 20%.

Figure 2 Evaluations based on 28 participants in the co-administration group in HZ/su and mRNA-1273 booster cohort risk assessment curve based on the proposed safety holding rules

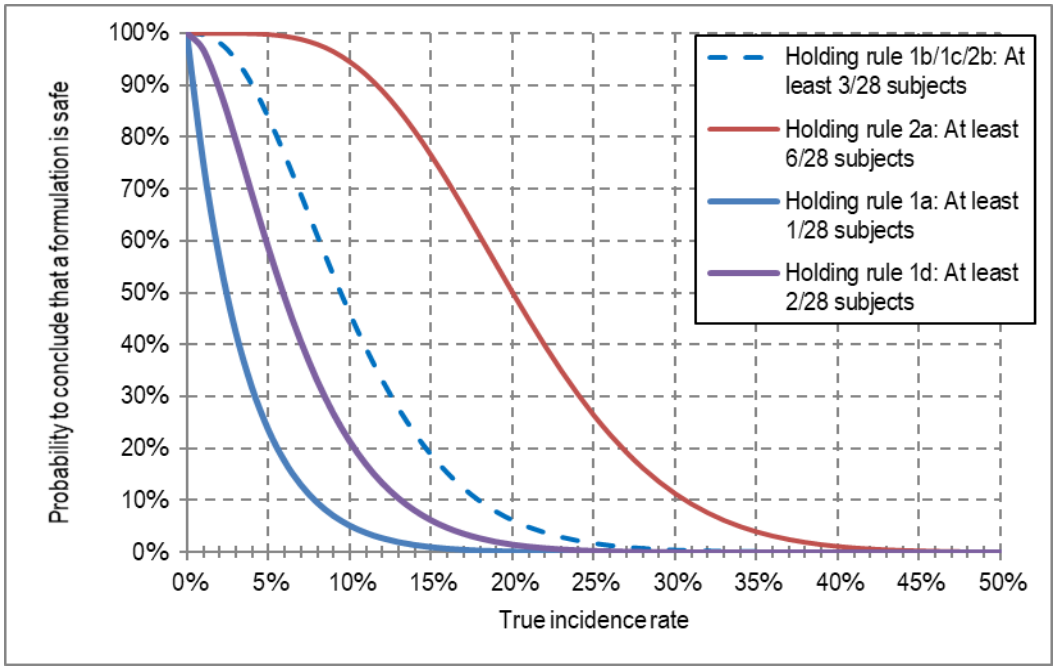
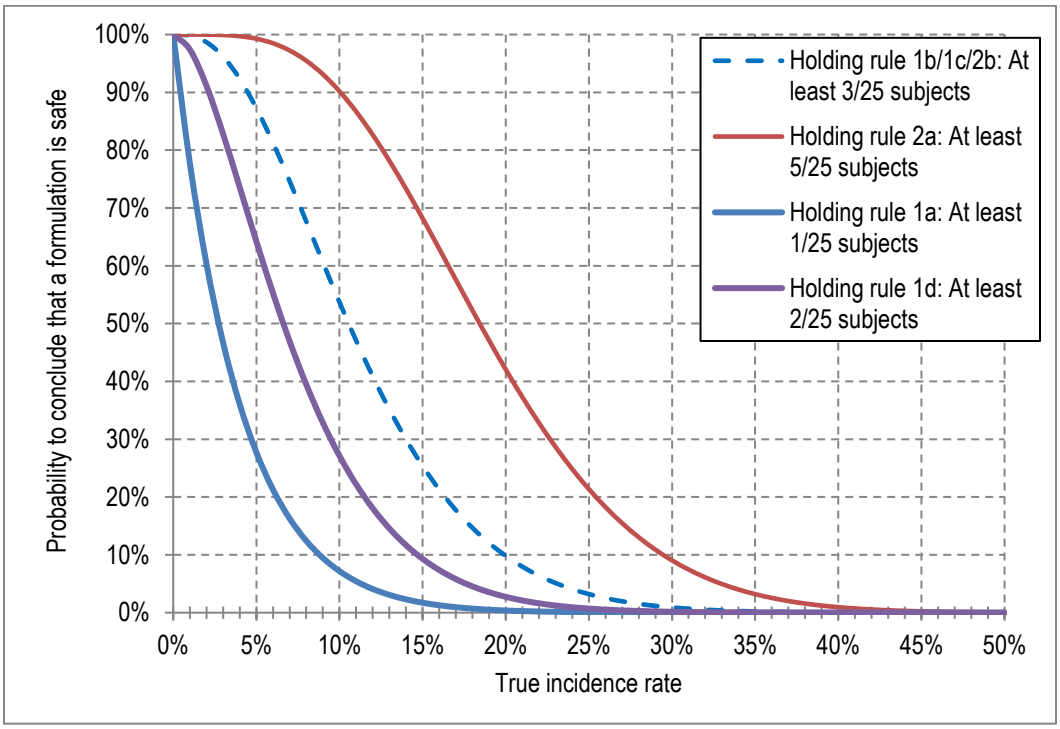


Figure 3 illustrates that, with 25 participants per study group in the Flu D-QIV and mRNA-1273 booster vaccine cohort at the pre-specified scheduled SRT review:

- Each holding rule 1a and 1d has more than 78% chance of not being met for vaccination with a true incidence rate of 1% and has more than 73% chance of being met for vaccination with a true incidence rate above 10%.
- Each holding rule 1b, 1c and 2b has 54% chance of not being met for vaccination with a true incidence rate below 10% and has 75% chance of being met for vaccination with a true incidence rate above 15%.

- Each holding rule 2a has more than 68% chance of not being met for vaccination with a true incidence rate below 15% and more than 58% chance of being met for vaccination with a true incidence rate above 20%.

Figure 3 Evaluations based on 25 participants in the co-administration group in Flu D-QIV and mRNA-1273 booster cohort risk assessment curve based on the proposed safety holding rules



8.3. Adverse events (AEs), serious adverse events (SAEs) and other safety reporting

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

The timeframes for collecting and reporting the safety information are provided in Table 14.

Table 14 Timeframes for collecting and reporting of safety information

EVENT	TIMING OF REPORTING
Local and systemic solicited events	Day 1 through Day 7 following each study intervention administration (see Figure 1)
Unsolicited AEs	Day 1 through Day 30 following each study intervention administration (see Figure 1)
AEs/SAEs leading to withdrawal from the study	Day 1 following study intervention administration through Phone Contact 2 study conclusion
All SAEs including SAEs related to the study intervention	Day 1 following study intervention administration through Phone Contact 2 study conclusion
AEs/SAEs related to study participation or SAEs related to concurrent GlaxoSmithKline medication/vaccine	Enrollment (i.e., signing ICF) through Phone Contact 2 study conclusion
IMCs, AESIs, COVID-19 cases, and in HZ/su and mRNA-1273 booster cohort only, also pIMDs and suspected HZ episodes	Day 1 following study intervention administration through Phone Contact 2 study conclusion
Pregnancy	Day 1 through Phone Contact 2 study conclusion

The investigator or designee will record and immediately report all SAEs/AESIs/pIMDs/pregnancies in study participants to PPD via the Expedited AE Reporting Form or pregnancy form (as applicable). Reporting should, under no circumstances, occur later than 24 hours after the investigator becomes aware of an SAE/AESI/pIMD/pregnancy, as indicated in Section 10.2.12. The investigator will submit any updated SAE/AESI/pIMD/pregnancy data to PPD 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 14. Investigators are not obligated to actively seek AEs or SAEs from 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 a study intervention, the investigator will promptly notify the study contact for reporting SAEs mentioned in Table 16.

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

Detection and recording of AEs/SAEs/AESIs/pIMDs/pregnancies are detailed in Section 10.2.10.

Assessment of AE/SAE/AESI/pIMD intensity, causality and outcome are described in Section 10.2.11.

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

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/AESI/pIMD/pregnancy, it must be reported to PPD using the required documentation and within the timeframes mentioned in Table 15. This is essential for meeting GSK and Moderna legal obligations and ethical responsibilities for participant safety and the safety of a study intervention under clinical investigation.

For SAEs/AESIs/pIMDs, the investigator must always provide an assessment of causality at the time of the initial report, as defined in the Section 10.2.11.2.

Local regulatory requirements, GSK and Moderna policy for preparation of an investigator safety report of Suspected Unexpected Serious Adverse Reactions (SUSAR) must be followed. These reports will be forwarded to investigators as necessary.

GSK and Moderna have the legal responsibility to notify both local and other applicable authorities/regulatory agencies about the safety of an investigational study intervention under their IND. GSK and Moderna will comply with country-specific regulatory requirements related to safety reporting to the regulatory authority, IRB and investigators.

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

Please refer to Section 10.2.12 for further details regarding the reporting of SAEs/AESIs/pIMDs/pregnancies.

Table 15 Timeframes for submitting SAE, AESI, pIMD, and pregnancy reports to PPD

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*	electronic pregnancy report	24 hours*	electronic pregnancy report
AESIs	24 hours**	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events 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 an AESI or pIMD.

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

Table 16 Contact information for reporting SAEs, AESIs, pIMDs, study holding rules and pregnancies

Study contact for questions regarding SAEs, AESIs, pIMDs, study holding rules, and pregnancies Refer to the local study contact information document
Back up study contact for reporting SAEs, AESIs, pIMDs, study holding rules, and pregnancies Available 24/24 hours and 7/7 days: 24 Hours Safety Hotline: +1 800 201 8725 +1 910 558 7104 24 Hour Safety Hotline Fax: +1 888 488 9697 +1 919 654 3849

8.3.4. Treatment of AEs

Any medication administered for the treatment of an SAE/AESI/pIMD should be recorded in the Expedited Adverse Event Report of the participant's eCRF screen (refer to Section 10.2.12.1).

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 always keep the participant card in their possession for the duration of the study. In an emergency, this card serves to inform the responsible attending physician/caregiver/family member that the participant is in a clinical study and that relevant information may be obtained by contacting the investigator or his/her back-up.

8.3.6. Medical device deficiencies

One of the study interventions, the seasonal influenza vaccine, Flu D-QIV, is presented as a pre-filled syringe and according to the FDA regulations [FDA, 2018] is within scope of device reporting in clinical trials as a combination product constituted of a device and biologic product (e.g., pre-filled syringes). Refer to the Glossary of terms for the definition of the combination product and medical device deficiencies. Device-related incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 10.4.

8.3.6.1. Detection, follow-up, and prompt reporting of medical device deficiency

The investigator is responsible for the detection, documentation and prompt reporting of any medical device deficiency occurring during the study to PPD. This applies to any medical device provided for the conduct of the study.

Device deficiencies will be reported to PPD within 24 hours after the investigator determines that the event meets the protocol definition of a device deficiency.

The investigator will ensure that follow-up includes any additional investigations to elucidate the nature and/or relatedness of the device deficiency to the incident. Follow-up applies to all participants, including those who discontinue study intervention or the study.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator and also reported to PPD.

Refer to Section 10.4 for definitions and details on recording and reporting of these events.

8.3.6.2. Regulatory reporting of medical device deficiency when used as combination product

The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study to PPD. GSK has a legal responsibility to notify appropriate regulatory authorities and other entities about safety information linked to medical devices being used in clinical studies. Refer to Section 10.4.3 for details of reporting.

The investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB.

8.4. Pharmacokinetics

Pharmacokinetics are not evaluated in this study.

8.5. Genetics

This section is not applicable.

8.6. Biomarkers

This section is not applicable.

8.7. Immunogenicity assessments

Immunogenicity is described in Section 8.1.

8.8. Health outcomes

This section is not applicable.

8.9. Study procedures during special circumstances

During special circumstances (e.g., COVID-19 pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be followed. For the duration of such special circumstances, the following measures may be implemented for enrolled participants:

- Safety follow-up may be made by a phone call, other means of virtual contact, or home visit, if appropriate.
- The eDiary device may be returned to the study center by conventional mail after the end of the relevant data collection period.
- Visits for suspected AEs may take place in a different location* other than the study center or at participant's home. If this is not feasible, then the medical evaluation of AEs may take place remotely with documentation of symptoms by other means of communication (e.g., phone call or videoconference), if possible.
- Biological samples may be collected at a different location* other than the study center or at participant's home. Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.

*Note: It is the investigator's responsibility to identify an alternate location. The investigator should ensure that this alternate location meets ICH Good Clinical Practice (GCP) requirements, such as adequate facilities to perform study procedures, appropriate training of the staff, and documented delegation of responsibilities in this location. This alternate location may need to be covered by proper insurance for the conduct of study on participants by investigator and study center staff other than the designated study center.

The impact on PPS eligibility will be determined on a case-by-case basis. If despite best efforts, it is not possible to collect the biological samples within the interval pre-defined in the protocol, or if it is not possible to administer the second dose of HZ/su as defined in the protocol, then the interval may be extended. Details will be provided in the Statistical Analysis Plan.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical hypotheses

The study will test 4 hypotheses under the primary objectives and 1 hypothesis under a secondary immunogenicity objective. The objectives will be assessed independently for the two cohorts (HZ/su and mRNA-1273 booster, Flu D-QIV and mRNA-1273 booster) at the first interim analysis. All the safety analyses under the secondary objective are descriptive and are described in Section 9.3.6.

Primary objectives for HZ/su and mRNA-1273 booster cohort:

Hypothesis 1: The null hypothesis for this primary objective under consideration is Upper Limit (UL) of 95% CI for adjusted GMC ratio between HZ/suSeq group and HZ/suCoAd group for anti-gE antibody concentration at 1 month post-dose 2 of HZ/su (at Week 14 for HZ/suSeq, at Week 12 for HZ/suCoAd) is ≥1.5.

Success criteria: The objective will be met if the UL of the 95% CI of the adjusted GMC ratio between HZ/suSeq and HZ/suCoAd group for anti-gE antibody concentration at 1 month post-dose 2 of HZ/su (at Week 14 for HZ/suSeq, at Week 12 for HZ/suCoAd) is <1.5.

Hypothesis 2: The null hypothesis for this primary objective under consideration is UL of 95% CI for adjusted GMC ratio between HZ/suSeq and HZ/suCoAd group for anti-S protein antibody concentration at 1 month post mRNA-1273 booster dose (at Week 4 for HZ/suSeq and HZ/suCoAd) is ≥ 1.5.

Success criteria: The objective will be met if the UL of the 95% CI of the adjusted GMC ratio between HZ/suSeq and HZ/suCoAd group for anti-S protein antibody at 1 month post mRNA-1273 booster dose (at Week 4 for HZ/suSeq and HZ/suCoAd) is <1.5.

Primary objectives for Flu D-QIV and mRNA-1273 booster cohort:

Hypothesis 3:- The null hypothesis for this primary objective under consideration is UL of 95% CI for adjusted GMT ratio between FluD-QIVSeq and FluD-QIVCoAd group for anti-HI antibody titer at 1 month post Flu D-QIV (at Week 6 for FluD-QIVSeq, at Week 4 for FluD-QIVCoAd) is ≥ 1.5.

Success criteria - The objective will be met if the UL of the 95% CI of the adjusted GMT ratio between FluD-QIVSeq and FluD-QIVCoAd group for anti-HI antibody titer at 1 month post Flu D-QIV (at Week 6 for FluD-QIVSeq, at Week 4 for FluD-QIVCoAd) is <1.5 for each strain included in the Flu D-QIV vaccine.

Hypothesis 4: The null hypothesis for this primary objective under consideration is UL of 95% CI for adjusted GMC ratio between FluD-QIVSeq and FluD-QIVCoAd group for anti-S protein antibody concentration at 1 month post mRNA-1273 booster dose (at Week 4 for FluD-QIVSeq and FluD-QIVCoAd) is ≥ 1.5.

Success criteria - The objective will be met if the UL of the 95% CI of the adjusted GMC ratio between FluD-QIVSeq and FluD-QIVCoAd group for anti-S protein antibody concentration at 1 month post mRNA-1273 booster dose (at Week 4 for FluD-QIVSeq and FluD-QIVCoAd) is <1.5.

Secondary objective for Flu D-QIV and mRNA-1273 booster cohort:

The secondary objective for the Flu D-QIV and mRNA-1273 booster cohort will be assessed once the primary objective for Flu D-QIV and mRNA-1273 booster cohort is demonstrated. This will not be used to confirm study success, rather, for informative purposes to support the primary endpoint.

Hypothesis 5: The null hypothesis for this secondary objective under consideration is UL of the 95% CI of the SCR difference between FluD-QIVSeq and FluD-QIVCoAd group at 1 month post Flu D-QIV (at Week 6 for FluD-QIVSeq, at Week 4 for FluD-QIVCoAd) is ≥ 10%.

Success criteria: The objective will be met if the UL of the 95% CI of the SCR difference between FluD-QIVSeq and FluD-QIVCoAd group at 1 month post Flu D-QIV (at Week 6 for FluD-QIVSeq, at Week 4 for FluD-QIVCoAd) is <10% for each strain included in the Flu D-QIV vaccine.

9.2. Analysis sets

The analysis sets defined in this study are provided in Table 17. As separate analysis presentations will be provided for the HZ/su and mRNA-1273 booster cohort and the Flu D-QIV and mRNA-1273 booster cohort, separate analysis sets are defined for each cohort.

In the HZ/su and mRNA-1273 booster cohort, the HZ/su and mRNA-1273 PPS will be used for analysis of hypothesis 1 and hypothesis 2. In the Flu D-QIV and mRNA-1273 booster cohort, the Flu D-QIV and mRNA-1273 PPS will be used for analysis of hypothesis 3, hypothesis 4, and hypothesis 5.

If, in any vaccine group, the percentage of vaccinated participants with serological results excluded from either PPS is 5% or more, a second analysis based on the HZ/su and mRNA-1273 Exposed set or Flu D-QIV and mRNA-1273 Exposed set will be performed to complement the Per-Protocol analysis.

Table 17 Analysis sets

Analysis set	Description
Enrolled Set	The enrolled set will include all participants who sign the informed consent.
Randomized set	The randomized set will include all participants from the enrolled set who are randomized.
HZ/su and mRNA-1273 Exposed Set	The HZ/su and mRNA-1273 Exposed set will include all participants in the HZ/su and mRNA-1273 booster cohort with at least 1 vaccine administration. The Exposed set analysis will be performed per vaccine(s) actually administered (at Day 1). The HZ/su and mRNA-1273 Exposed set for analysis of immunogenicity will include vaccinated participants for whom immunogenicity data are available.
HZ/su and mRNA-1273 PPS (For Hz/su and mRNA-1273 booster cohort)	The HZ/su and mRNA-1273 PPS will include all participants from the HZ/su and mRNA-1273 Exposed set Who meet all eligibility criteria; Who receive all doses of study interventions according to their random assignment; For whom administration site of study vaccine is known; Who do not receive any other prohibited concomitant medication/vaccine up to blood sample post HZ/su dose 2. Who comply with the procedures and intervals defined in the protocol and allowed for analysis up to blood sample post HZ/su dose 2; Who do not meet any of the criteria for elimination up to blood sample post HZ/su dose 2; For whom data concerning immunogenicity endpoint measures are available at post vaccination for either mRNA-1273 booster or HZ/su dose 2.
Flu D-QIV and mRNA-1273 Exposed Set (For Flu D-QIV and mRNA-1273 booster cohort)	The Flu D-QIV and mRNA-1273 Exposed set will include all participants in the Flu D-QIV and mRNA-1273 booster cohort with at least 1 vaccine administration documented. The Exposed set analysis will be performed per vaccine(s) actually administered (at Day 1). The Flu D-QIV and mRNA-1273 Exposed set for analysis of immunogenicity will include vaccinated participants for whom immunogenicity data are available.
Flu D-QIV and mRNA-1273 PPS (For Flu D-QIV and mRNA-1273 booster cohort)	The Flu D-QIV and mRNA-1273 PPS will include all participants from the Flu D-QIV and mRNA-1273 Exposed set Who meet all eligibility criteria; Who receive all doses of study interventions according to their random assignment; For whom administration site of study vaccine is known; Who do not receive any other prohibited concomitant medication/vaccine. Who comply with the procedures and intervals defined in the protocol and allowed for analysis; Who do not meet any of the criteria for elimination during the study through the last blood sample for the group; For whom data concerning immunogenicity endpoint measures are available at post vaccination for either mRNA-1273 booster or Flu D-QIV.

9.2.1. Criteria for elimination from analysis

Participants may be eliminated from the PPS in their respective cohort, if, during the study up to blood sampling timepoint post last dose, they incur a condition that has the capability of altering their immune response (i.e., an IMC) or are confirmed to have an alteration of their initial immune status. Refer to Glossary of terms for the definition of intercurrent medical conditions. More details on other reasons for elimination will be presented in the SAP.

9.3. Statistical analyses

9.3.1. Statistical analysis plan

The SAP will be developed and finalized before First Participant First Visit (FPFV) and will describe the participant analysis sets to be included in the analyses and procedures for accounting for missing, unused, and spurious data.

This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

Unless otherwise mentioned, for all the planned analyses with CI, a 95% CI will be computed.

9.3.2. General considerations

During special circumstances (e.g., the COVID-19 pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare will be followed. For the duration of such special circumstances, some measures may impact the data and analysis (e.g., missing visits, early study discontinuation). The impact will be determined on a case by case basis and the analysis methodology described in the SAP will account for such cases, if any.

9.3.3. Participants disposition

Number of screened, enrolled, exposed (at least 1 study intervention, full study intervention course), and eligible for the PPS included in each cohort, group and overall will be described.

9.3.4. Primary endpoints analysis

The primary endpoints related to immunogenicity analysis are described in Section 3, Objectives and Endpoints.

Differing analysis sets (refer to Section 9.2) will apply to each primary endpoint.

9.3.4.1. Primary endpoints for HZ/su and mRNA1273 booster study cohort

9.3.4.1.1. HZ/su immunogenicity post-dose 2 (anti-gE antibodies)

The immunogenicity assessment of the HZ/su primary endpoint (Hypothesis 1 stated in Section 9.1) will be summarized on the HZ/su and mRNA-1273 PPS.

Anti-gE antibody concentrations will be expressed as a between-group GMC ratio at 1 month post-dose 2 of HZ/su (at Week 14 for HZ/suSeq, at Week 12 for HZ/suCoAd) and will be summarized.

For anti-gE at 1 month post-dose 2 of HZ/su, the 95% CI of the between-group GMC ratios will be computed using an analysis of covariance (ANCOVA) model on the log10 transformation of the concentrations. The age strata (50-59, 60-69, ≥70 YOA) and pre-vaccination log-transformed antibody concentrations will be included as covariates and vaccine group will be included as a fixed effect.

9.3.4.1.2. mRNA-1273 booster immunogenicity (anti-S protein antibodies)

The immunogenicity assessment of the mRNA-1273 booster primary endpoint (Hypothesis 2 stated in Section 9.1) will be summarized on the HZ/su and mRNA-1273 PPS

Anti-S Protein antibody concentrations will be expressed as a between-group GMC ratio at 1 month post mRNA-1273 booster dose (at Week 4 for both groups, HZ/suSeq and HZ/suCoAd).

For anti-S Protein at 1 month post mRNA-1273 booster dose, the 95% CI of the between-group GMC ratios will be computed using an analysis of covariance (ANCOVA) model on the log10 transformation of the concentrations. The age strata (50-59, 60-69, ≥70 YOA) and pre-vaccination log-transformed antibody concentrations will be included as covariates and vaccine group will be included as a fixed effect.

Pending final assay evaluations and validations prior to study specimen testing, anti-S protein may be replaced with SARS-CoV-2 neutralizing antibody titers in which case, GMT ratios will be used in the analysis described above.

9.3.4.2. Primary endpoints for Flu D-QIV and mRNA-1273 booster study cohort

9.3.4.2.1. Flu D-QIV immunogenicity (anti-HI antibodies)

The immunogenicity assessment of the Flu D-QIV primary endpoint (Hypothesis 3 stated in Section 9.1) will be summarized on the Flu D-QIV and mRNA-1273 PPS.

Anti-HI antibody titers against the 4 influenza strains included in Flu D-QIV will be expressed as a between-group GMT ratio at 1 month post Flu D-QIV (at Week 6 for FluD-QIVSeq, at Week 4 for FluD-QIVCoAd).

To demonstrate non-inferiority of Flu D-QIV in terms of anti-HI antibody GMTs, the 95% CI of the between-group GMT ratios post-dose 1 of Flu D-QIV will be computed using an ANCOVA model on the log10 transformation of the titers. The pre-vaccination log-transformed antibody titers and age strata (18-64, ≥65 YOA) will be included as covariates and vaccine group will be included as a fixed effect. This will be done for each of the 4 strains included in the Flu D-QIV vaccine.

9.3.4.2.2. mRNA-1273 booster immunogenicity (anti-S protein antibodies)

The immunogenicity assessment of the mRNA-1273 primary endpoint (Hypothesis 4 stated in Section 9.1) will be summarized for the Flu D-QIV and mRNA-1273 PPS

Anti-S Protein antibody concentrations will be expressed as a between-group GMC ratio at 1 month post mRNA-1273 booster dose (at Week 4 for FluD-QIVSeq and FluD-QIVCoAd).

For anti-S Protein at 1 month post mRNA-1273 booster dose, the 95% CI of the between-group GMC ratios will be computed using an analysis of covariance (ANCOVA) model on the log10 transformation of the concentrations. The pre-vaccination log-transformed antibody concentrations and age strata (18-64, ≥65 YOA) will be included as covariates and vaccine group will be included as a fixed effect.

9.3.5. Secondary immunogenicity endpoints analyses

9.3.5.1. Flu D-QIV immunogenicity (Anti-HI antibody SCRs)

The immunogenicity assessment of the Flu D-QIV secondary endpoint (Hypothesis 5 stated in Section 9.1) will be summarized for the Flu QIV and mRNA-1273 PPS

Anti-HI antibody SCRs against the 4 influenza strains will be summarized by group (FluD-QIVSeq and FluD-QIVCoAd).

To demonstrate non-inferiority of Flu D-QIV in terms of HI antibody SCRs for each strain, the difference between the SCR and the 95% CI for the difference in SCR in the FluD-QIVSeq group as compared to the FluD-QIVCoAd group at 1 month post Flu D-QIV (at Week 6 for FluD-QIVSeq, at Week 4 for FluD-QIVCoAd) will be evaluated.

The 2-sided 95% confidence interval (CI) on group difference in seroconversion rate will be computed based on the method of Miettinen and Nurminen [Miettinen, 1985].

9.3.5.2. Descriptive immune endpoints

9.3.5.2.1. Anti-gE humoral immunogenicity at pre-vaccination and post-dose 2 of HZ/su

Descriptive statistics (including 95% CIs) of the following anti-gE humoral immunogenicity parameters will be provided by group and by age category (50-59, 60-69, ≥ 70 YOA). Analyses at 1 month post-dose 2 of HZ/su will use the HZ/su and mRNA-1273 PPS.

- VRR with exact 95% CI at 1 month post-dose 2 of HZ/su (at Week 14 for HZ/suSeq, at Week 12 for HZ/suCoAd)
  - The VRR for anti-gE post-dose 2 is defined as the percentage of participants who have at least:
    - A 4-fold increase in the post-dose anti-gE antibodies concentration as compared to the pre-vaccination anti-gE antibodies concentration, for participants who are seropositive at pre-vaccination, or,

- A 4-fold increase in the post-dose anti-gE antibodies concentrations as compared to the anti-gE antibodies cut-off value for seropositivity, for participants who are seronegative at pre-vaccination.

This will be summarized by participants who are seronegative at pre-vaccination, seropositive at pre-vaccination and overall status at pre-vaccination (seronegative or seropositive)

- Seropositivity rate with exact 95% CI at pre-vaccination (at Day 1 for HZ/suCoAd, at Week 2 for HZ/suSeq) and at 1 month post-dose 2 of HZ/su (at Week 14 for HZ/suSeq, at Week 12 for HZ/suCoAd). Seropositivity is defined as the percentage of participants whose antibody concentration is greater than or equal to the assay cut-off value (97 mIU/mL).
- Anti-gE antibody concentrations expressed as GMC with 95% CI at pre-vaccination (at Day 1 for HZ/suCoAd, at Week 2 for HZ/suSeq) and at 1 month post-dose 2 of HZ/su (at Week 14 for HZ/suSeq, at Week 12 for HZ/suCoAd). GMC calculations will be performed by taking the anti-log of the mean of the log concentration transformations. Anti-gE antibody concentrations will be displayed using reverse cumulative curves.
- MGI from pre-vaccination with 95% CI at 1 month post-dose 2 of HZ/su (at Week 14 for HZ/suSeq, at Week 12 for HZ/suCoAd).
- Descriptive statistics of fold increase from baseline for anti-gE antibody ELISA concentrations
- The distribution of the fold increase i.e. percentage of participants with a more than X-fold (e.g. >2, >4, >6,...-fold) increase along with 95% CI will be presented.

9.3.5.2.2. mRNA-1273 booster dose humoral immunogenicity

Descriptive statistics (including 95% CIs) of the following mRNA-1273 booster immunogenicity parameters will be provided by group and by age category (50-59, 60-69, ≥ 70 YOA for HZ/su and mRNA-1273 booster cohort, 18-64, ≥ 65 YOA for Flu D-QIV and mRNA-1273 booster cohort). All summaries will be provided for the HZ/su and mRNA-1273 PPS and for the Flu D-QIV and mRNA-1273 PPS in the respective cohorts.

- Anti-S Protein antibody concentrations expressed as GMC with 95% CIs by group at pre-vaccination (Day 1) and 1 month post mRNA-1273 booster dose (at Week 4 for all groups including HZ/suSeq, HZ/suCoAd, FluD-QIVSeq, FluD-QIVCoAd and overall). The GMC calculations will be performed by taking the anti-log of the mean of the log concentration transformations. Anti-S protein antibody concentrations will be displayed using reverse cumulative curves.
- MGI with 95% CI at 1 month post mRNA-1273 booster dose (at Week 4 for all groups).

Pending final assay evaluations and validations prior to study specimen testing, anti-S protein may be replaced with SARS-CoV-2 neutralizing antibody titers in which case, GMTs will be used in the analysis described above.

9.3.5.2.3. Flu D-QIV humoral immunogenicity

Descriptive statistics, including 95% CIs, will be produced for the following Flu D-QIV humoral immunogenicity parameters for each of the 4 influenza vaccine strains by group and age categories (18-64, ≥ 65 YOA). Summaries will be produced for the Flu D-QIV and mRNA-1273 PPS.

- Anti-HI antibody titers against the 4 influenza strains included in Flu D-QIV expressed as GMTs with 95% CIs at pre-vaccination and at 1 month post Flu D-QIV (at Week 6 for FluD-QIVSeq, at Week 4 for FluD-QIVCoAd). GMT calculations will be performed by taking the anti-log of the mean of the log titer transformations. Anti-HI antibody titers will be displayed using reverse cumulative curves.

  SPR with exact 95% CIs at pre-vaccination and at 1 month post Flu D-QIV (at Week 6 for FluD-QIVSeq, at Week 4 for FluD-QIVCoAd). SPR is defined as the percentage of participants with a serum HI titer ≥ 1:40.
- Seropositivity rates with exact 95% CIs at pre-vaccination and at 1 month post Flu D-QIV (at Week 6 for FluD-QIVSeq, at Week 4 for FluD-QIVCoAd).
- MGI from pre-vaccination with 95% CIs at 1 month post Flu D-QIV (at Week 6 for FluD-QIVSeq, at Week 4 for FluD-QIVCoAd). MGI is defined as the geometric mean of the within participant ratios of the post-vaccination reciprocal HI titer to the Day 1 reciprocal HI titer.
- SCR with exact 95% CIs at 1 month post Flu D-QIV (at Week 6 for FluD-QIVSeq, at Week4 for FluD-QIVCoAd). SCR is defined as the percentage of participants who have either a pre-vaccination titer < 1:10 and a post-vaccination titer ≥ 1:40 or a pre-vaccination titer ≥ 1:10 and at least a 4 fold increase in post-vaccination titer.

The assessment of SPR and SCR will also be performed by age categories (18-64, ≥65 YOA) descriptively based on the following CBER criteria:

- The lower limit of the 95% confidence interval for SPR should be ≥ 70% in participants aged 18-64 YOA or ≥ 60% in participants ≥ 65 YOA.
- The lower limit of the 95% confidence interval for SCR should be ≥ 40% in participants aged 18-64 YOA or ≥ 30% in participants ≥ 65 YOA.

At least one of the 4 strains must meet the criteria above for SPR and SCR to be considered as having met CBER criteria.

9.3.6. Secondary endpoints analyses

The safety endpoints will be summarized on the HZ/su and mRNA-1273 Exposed set and on the Flu D-QIV and mRNA-1273 Exposed Set. The analyses will be descriptive. Subgroup analyses may be performed and will be detailed in the statistical analysis plan (SAP).

9.3.6.1. Solicited local and systemic AEs

The percentage of participants with at least 1 solicited local event, with at least 1 solicited systemic event and any solicited event during the 7-day follow-up period will be tabulated, for each vaccination visit and overall, with exact 95% CIs. Similar summaries will be provided for Grade 3 events

The number and percentage of participants reporting each solicited local and solicited systemic AE during the solicited 7-day follow-up period will be tabulated with exact 95% CIs after each vaccination visit and overall per participant for all study groups (HZ/suSeq, HZ/suCoAd, FluD-QIVSeq, FluD-QIVCoAd and overall).

- Solicited local events (intensity [any grade, Grade 3], resulting in medically attended visit) during the 7-day follow-up period after each intervention administration will be summarized. Any events ongoing beyond the 7-day post-vaccination period, following each vaccination visit and overall will also be tabulated for each vaccine separately.
- Solicited systemic events (intensity [any grade, Grade 3], and resulting in a medically attended visit) during the 7-day follow-up period after each vaccination visit will be summarized. Any events ongoing beyond the 7-day post-vaccination period, following each vaccination visit and overall will also be tabulated for each vaccine separately.
- The duration of the solicited AEs, both local (for each vaccine separately) and systemic, during the 7-day follow-up period after each vaccination visit and overall (total duration) will be calculated and summarized by mean, median, standard deviation, and range.

9.3.6.2. Unsolicited AEs

The number and percentage of participants reporting unsolicited AEs classified by MedDRA primary System Organ Class (SOC) and Preferred Term (PT) will be summarized along with exact 95% CIs during:

- The 14-day post-vaccination period after each and any vaccination visit for all study groups and
- The 30-day post-vaccination period after each and any vaccination visit. It should be noted that participants in the HZ/suSeq and FluD-QIVSeq groups will receive their HZ/su or Flu D-QIV, respectively, at Day 14 post mRNA booster vaccine dose at Day 1.

Unsolicited AEs will also be presented by intensity (any grade and Grade 3), any related, Grade 3 related, Grade 3 non-serious, Grade 3 non-serious related, and resulting in a medically-attended visit.

9.3.6.3. SAEs

Number and percentage of participants reporting SAEs and fatal SAEs from first vaccination up to 30 days post-last vaccination and from first vaccination up to study end

will be summarized for all study groups (HZ/suSeq, HZ/suCoAd, FluD-QIVSeq, FluD-QIVCoAd and overall). Any related SAEs will also be presented for all study groups (HZ/suSeq, HZ/suCoAd, FluD-QIVSeq, FluD-QIVCoAd and overall). Fatal SAEs will be presented by onset day and day of death, for both any fatal SAEs and any related fatal SAEs. All SAEs will be summarized by MedDRA SOC and PT. SAEs, fatal SAEs and withdrawals due to SAEs will also be listed.

9.3.6.4. Potential Immune-mediated Diseases (for HZ/su and mRNA-1273 booster cohort only)

Number and percentage of participants reporting pIMDs from first vaccination up to 30 days post-last vaccination and from first vaccination up to study end will be summarized for all study groups (HZ/suSeq, HZ/suCoAd, overall). All pIMDs will be summarized by MedDRA SOC and PT. pIMDs will also be listed. Any related pIMD will also be presented for study groups (HZ/suSeq, HZ/suCoAd and overall).

9.3.6.5. Adverse events of special interest

Number and percentage of participants reporting AESIs from first vaccination up to 30 days post-last vaccination and from first vaccination up to study end will be summarized for all study groups. All AESIs will be summarized by MedDRA SOC and PT. A listing of AESIs will also be presented.

9.3.6.6. Suspected HZ episodes (for HZ/su and mRNA-1273 booster cohort only)

Number and percentage of participants reporting suspected HZ episodes from first dose to study end will be summarized for the HZ/suSeq and HZ/suCoAd study groups and overall. Potential HZ episodes throughout the entire study period will be listed by MedDRA PT.

9.3.6.7. COVID-19 cases

Number and percentage of participants meeting the case definitions of COVID-19 from first dose to study end will be summarized for all study groups (HZ/suSeq, HZ/suCoAd, FluD-QIVSeq, FluD-QIVCoAd and overall) and COVID-19 cases will also be listed.

9.3.6.8. Pregnancies

A listing of participants with confirmed pregnancies from first dose to study end will be provided for all study groups along with pregnancy details.

9.3.6.9. Withdrawals due to AEs and SAEs

Withdrawals due to solicited AEs, both local and systemic, unsolicited AEs, and SAEs will be presented in a listing.

9.3.7. Exploratory endpoints analyses

Anti-gE humoral immunogenicity at post-dose 1 of HZ/su:

Anti-gE antibody testing post-dose 1 may be limited, based upon the nature of the responses observed following the second dose of HZ/su and scientific relevance. Similar descriptive statistics will be presented for these results at 1 month post-dose 1 of HZ/su as described in Section 9.3.5.2.1.

Confirmed HZ cases (for HZ/su and mRNA-1273 booster cohort only):

- Number and percentage of participants reporting clinically confirmed HZ cases by PCR from first vaccination up to study end will be summarized for all study groups (HZ/suSeq, HZ/suCoAd, and overall).

Neutralizing antibodies (assuming if not assessed as a primary endpoint in all participants):

- GMT with 95% CI of SARS-CoV-2 neutralizing antibody concentrations in a sub-cohort of participants in each study group (HZ/suSeq, HZ/suCoAd, FluD-QIVSeq, FluD-QIVCoAd and overall) at pre-vaccination and 1 month post mRNA-1273 booster (at Week 4 for all groups). The sub-cohort (approximately 50 evaluable participants) will be selected post-hoc, based on other observed immune assay results.

Descriptive humoral immune responses to vaccination and/or SARS-CoV-2 infection:

- GMCs with 95% CI of anti-RBD protein antibodies at pre-vaccination and at 1 month post mRNA-1273 booster (at Week 4 for all study groups [HZ/suSeq, HZ/suCoAd, FluD-QIVSeq, FluD-QIVCoAd and overall]).

Descriptive humoral immune responses to SARS-CoV-2 infection:

- Anti-N seroconversion rate with exact 95% CI from pre-vaccination to 1 month post mRNA-1273 booster dose (at Week 4 for all study groups). Seroconversion is defined as a participant who is seronegative at baseline and seropositive post-vaccination OR for a participant seropositive at baseline, a 4-fold or more increase post-vaccination.

9.3.8. Other analyses

9.3.8.1. Demography and baseline characteristics analyses

For the HZ/su and mRNA-1273 booster study cohort, summaries of demographic characteristics will be produced for the HZ/su and mRNA-1273 Exposed Set and HZ/su and mRNA-1273 PPS by study group (HZ/suSeq and HZ/suCoAd and overall [i.e. both HZ/su groups]).

For the Flu D-QIV and mRNA-1273 booster study cohort, summaries of demographic characteristics will be produced for the Flu D-QIV and mRNA-1273 Exposed Set and Flu D-QIV and mRNA-1273 PPS by study group (FluD-QIVSeq, FluD-QIVCoAd and overall [i.e. both Flu D-QIV groups]).

Demographic characteristics (age at intervention in years, age category [50-59, 60-69, ≥70YOA for HZ/su and mRNA-1273 booster cohort; 18-64, ≥65 YOA for Flu D-QIV and mRNA-1273 booster cohort] sex, and race and ethnicity) will be summarized by group using descriptive statistics:

- Frequency tables will be generated for categorical variables such as race.
- Mean, median, standard error, and range will be provided for continuous data such as age.

Withdrawal status will be summarized by study group using descriptive statistics for the HZ/su and mRNA-1273 Exposed Set and Flu D-QIV and mRNA-1273 Exposed Set only:

- The number of participants enrolled into the trial as well as the number of participants excluded from per-protocol analyses will be tabulated along with reasons for elimination. A listing of protocol deviations will be provided.
- CONSORT tables will be generated to show the dispositions of participants from the enrolled set to the exposed sets and from the exposed sets to the per protocol sets.
- The numbers of withdrawn participants will be tabulated according to the reason for withdrawal.

The percentage of participants using a concomitant medication/vaccination during the 7-day follow-up period and during the 30-day follow-up period after each intervention administration will be summarized.

9.4. Interim analyses

9.4.1. Sequence of analyses

The SRT will first review safety and reactogenicity data reported up to 7 days post-dose 1 of HZ/su when 10% of participants in the HZ/suCoAd group and 7 days post Flu D-QIV when 5% of participants in the FluD-QIVCoAd group have been vaccinated. Selected tabulations will be generated for SRT review to decide on continuation of enrollment in the co-administration groups. Limited safety analyses will be performed after all participants in the HZ/su and mRNA-1273 booster cohort sequential group have completed 14 days of follow-up after their HZ/su dose 1, and when all participants in the Flu D-QIV and mRNA-1273 cohort sequential group have completed 14 days of follow-up after their Flu D-QIV dose. Periodic analyses will be done for regular SRT review. All SRT analyses will be descriptive.

In addition to the SRT review, 1 formal interim analysis of safety, reactogenicity, and immunogenicity is planned.

9.4.2. First interim analysis

The first interim analysis will include analysis of safety, reactogenicity, and immunogenicity when the last participant enrolled in the HZ/su and mRNA-1273 booster cohort completes 6 weeks post-dose 2 of HZ/su Phone Contact 1. These participants will

also have completed the 4 weeks of follow-up post mRNA-1273 booster vaccine visit. Participants in the Flu D-QIV cohort will have also completed 4 weeks of follow-up post Flu D-QIV and post mRNA-1273 booster vaccine at this stage.

Analysis will be performed on data as clean as possible and clinical study report will be provided. Individual participant listings will be provided at this stage.

The first interim analysis will include:

- The assessment of non-inferiority of the humoral immune response to Dose 2 of HZ/su (HZ/suSeq and HZ/suCoAd groups).
- The assessment of non-inferiority of the humoral immune response to Flu D-QIV (FluD-QIVSeq and FluD-QIVCoAd groups).
- The assessment of non-inferiority of the humoral immune response to mRNA-1273 booster dose (both cohorts [HZ/su, Flu D-QIV], all groups [HZ/suSeq, HZ/suCoAd, FluD-QIVSeq, FluD-QIVCoAd]) (when co-administered with HZ/su and when co-administered with Flu D-QIV).
- Reactogenicity data after each administered vaccine dose (All groups: All doses of Flu D-QIV and mRNA-1273 booster dose; and all doses of HZ/su).
- Unsolicited AEs (serious and non-serious) safety data will also be included up to 30 days follow-up post each dose (All groups; including post all doses of Flu D-QIV and mRNA-1273 booster dose; and post all doses of HZ/su).
- SAEs, pIMDs, AESIs, suspected HZ episodes, IMCs, COVID-19 cases and pregnancies until the Data Lock Point (DLP) for all groups.

9.4.3. Final analysis

The **final analysis** will include safety follow-up up to 6 months post the last vaccine dose. At that time, an integrated study report will be written. Individual participant listings will be available at this stage.

9.4.4. Statistical considerations for interim analysis

Refer to Section 9.1 for details on type I error adjustments.

Hypothesis testing at the first interim analysis will occur in parallel within each cohort. The assessment of success for the confirmatory immunogenicity objective in the HZ/su and mRNA-1273 booster cohort will be made at the first interim analysis. Similarly, the determination of success for the confirmatory immunogenicity objective for the Flu D-QIV and mRNA-1273 booster cohort will be made at the first interim analysis.

9.5. Sample size determination

Assumptions used for the sample size calculations come from data available from prior studies ZOSTER-004 (117036), ZOSTER-042 (116887), ZOSTER-035 (116889), ZOSTER-048 (201198), ZOSTER-059 (204487), FLU D-QIV-008 (114269), FLU D-QIV-010 PRI (117276), and EXPLO-CRD-004, as well as preliminary mRNA-1273 Phase I and Phase II data [Jackson, 2020; Chu, 2021].

After final assay evaluations and validations, should the primary mRNA-1273 endpoint be replaced by SARS-CoV-2 neutralizing antibody titers, the same assumptions will be made since the standard deviation used for calculations was at the upper range of what has been observed for both endpoints; thus, the sample sizes presented below will remain for each cohort.

The type I error to be maintained is 0.025 (one-sided) for each study cohort (HZ/su and mRNA-1273 booster, Flu D-QIV and mRNA-1273 booster). Study success will be evaluated separately for each cohort. For the HZ/su and mRNA-1273 booster cohort, non-inferiority must be achieved for both hypothesis 1 and hypothesis 2. For the Flu D-QIV and mRNA-1273 booster cohort, success must be achieved for both hypothesis 3 and hypothesis 4.

A total of 1546 participants will need to be enrolled and randomized between the 2 cohorts.

9.5.1. Sample size for HZ/su and mRNA-1273 study cohort

The global power considers meeting the primary objectives in the HZ/su and mRNA-1273 booster cohort – with 245 evaluable participants in the HZ/suCoAd and HZ/suSeq groups the global power is approximately 90%. A GMC ratio of 1.1 between HZ/suSeq and HZ/suCoAd is assumed. Assuming 10% of the participants randomized are non-evaluable (e.g. due to drop out/protocol violation), approximately 546 participants will need to be randomized (273 participants each in the HZ/suCoAd and HZ/suSeq groups).

Note: If the dose of mRNA-1273 booster is adjusted while the study is ongoing, the sample size will be compensated in this cohort to ensure that there are enough evaluable participants in each group. (Amended 21 September 2021)

Sample size calculations for the HZ/su and mRNA-1273 booster study cohort can be found in Table 18.

Table 18 Sample size calculations for HZ/su and mRNA-1273 booster study cohort

Endpoint	Number of Evaluable Participants per Cohort	α	Standard Deviation	Reference δ Assumed	NI δ	Total β	Power
***Post dose 2 HZ/su* Non-inferiority* (1-sided test) – Primary Endpoint**							
Post-Dose 2 GMC Ratio (Sequential vs. Co-Ad) anti-gE	245	0.025	0.35	1.1	1.5	1.1%	98.9%
***mRNA-1273 booster vaccine: Non-inferiority* (1-sided test) – Primary Endpoint**							
GMC Ratio (Sequential vs. Co-Ad) anti-S	245	0.025	0.45	1.1	1.5	8.9%	91.1%
Global β to show non-inferiority of the primary endpoints						~10%	
Global power for the primary endpoints							~90%

Co-Ad = co-administered; GMC = geometric mean concentration
* Pass 2019: alpha = 2.5% for HZ/su and mRNA-1273 booster GMC ratio; Non-Inferiority -Two Independent Means – Two-sample T-tests for Non-Inferiority Assuming Equal Variance
For gE and mRNA-1273 booster vaccine: non-inferiority limit = 0.176 (=log10(1.5)), reference limit = 0.0413 (=log10(1.1)).

SDs for HZ/su Dose 2 are taken from the average of the reference co-administration studies ZOSTER-004 (117036), ZOSTER-042 (116887), ZOSTER-035 (116889), ZOSTER-048 (201198), ZOSTER-059 (204487), FLU D-QIV-008 (114269), FLU D-QIV-010 PRI (117276), and EXPLO-CRD-004. SDs for mRNA-1273 booster are taken from preliminary mRNA-1273 Phase I and II data.

9.5.2. Sample size for Flu D-QIV and mRNA-1273 booster study cohort

The non-inferiority of Flu D-QIV using GMTs (hypothesis 3) will be tested with a 1-sided type I error of 0.025 for all 4 strains in the Flu D-QIV vaccine. No adjustment is needed for the type I error due to multiple comparison of Flu D-QIV 4 strains since one wants to reject the null hypothesis if one comparison is not conclusive.

The non-inferiority of Flu D-QIV using SCR difference for 4 strains (Flu D-QIV and/mRNA-1273 booster cohort secondary endpoint, hypothesis 5) will be tested using a sequential approach, meaning, hypothesis 3 and 4 (GMT, Flu D-QIV and mRNA-1273 booster primary endpoint) must be tested and non-inferiority of Flu D-QIV and mRNA-1273 booster using GMT ratio must be demonstrated before hypothesis 5 is tested. Both tests will use a type I error of 0.025. Study success on the Flu D-QIV and mRNA-1273 booster cohort will be declared if hypothesis 3 and 4 are met. Therefore, the power to achieve success for Flu D-QIV and mRNA-1273 booster cohort is driven by primary objectives for the Flu D-QIV and mRNA-1273 booster cohort.

A GMC ratio of 1.1 between FluD-QIVSeq and FluD-QIVCoAd is assumed for the mRNA endpoint. A GMT ratio of 1.04 between FluD-QIVSeq and FluD-QIV is assumed for the flu endpoint. The global power considers meeting both primary objectives in the Flu D-QIV and mRNA-1273 booster cohort –with 450 evaluable participants in the FluD-QIVCoAd and FluD-QIVSeq groups it is approximately 90.9%.

The nominal power for the secondary objective to demonstrate non-inferiority in terms of SCR difference for each strain in the Flu D-QIV vaccine between FluD-QIVSeq and FluD-QIVCoAd groups is at least 85%. Assuming 10% of the participants randomized are non-evaluable (e.g. due to drop out/protocol violation), approximately 1000 participants will need to be randomized (500 participants each in the FluD-QIVCoAd and FluD-QIVSeq groups).

Sample size calculations for the Flu D-QIV and mRNA-1273 booster study cohort can be found in Table 19.

Table 19 Sample size calculations for Flu D-QIV and mRNA-1273 booster study cohort

Primary Endpoint	Number of Evaluable Participants per Group	α	Standard Deviation	Reference δ Assumed	NI δ	Total β	Power
FLU D-QIV Non-inferiority* (1-sided test) – 4 Strains – Primary Endpoint on GMT ratio							
GMT Ratio (Sequential vs. Co-Ad) – A/ H1N1 strain	450	0.025	0.6	1.04	1.5	2.2%	97.8%
GMT Ratio (Sequential vs. Co-Ad) – A/H3N2 strain	450	0.025	0.6	1.04	1.5	2.2%	97.8%
GMT Ratio (Sequential vs. Co-Ad) – B/Victoria lineage	450	0.025	0.6	1.04	1.5	2.2%	97.8%
GMT Ratio (Sequential vs. Co-Ad) – B/Yamagata lineage	450	0.025	0.6	1.04	1.5	2.2%	97.8%
mRNA-1273 booster vaccine: Non-inferiority* (1-sided test) – Primary Endpoint							
GMC Ratio (Sequential vs. Co-Ad)	450	0.025	0.45	1.1	1.5	0.6%	99.4%
Global β to show non-inferiority of the primary endpoints						~9.1%	
Global power for the primary endpoints							**~90.9%**

FLU D-QIV Non-inferiority* (1-sided test) – 4 Strains – Secondary Endpoint on SCR difference						
Secondary Endpoint	**Number of Evaluable Participants per Group**	**α**	**Threshold**	**SCR Assumed**	**Total b**	**Power**
SCR difference (Sequential vs. Co-Ad) – A/H1NI strain	450	0.025	10%	78.6%	4.5%	95.5%
SCR difference (Sequential vs. Co-Ad) – A H3N2 strain	450	0.025	10%	70.3%	9.2%	90.8%
SCR difference (Sequential vs. Co-Ad) – B/Victoria lineage	450	0.025	10%	53.8%	14.9%	85.1%
SCR difference (Sequential vs. Co-Ad) B/Yamagata lineage	450	0.025	10%	56.9%	14.0%	86.0%

GMT = geometric mean titer; SCR = seroconversion rate

* Pass 2019: alpha = 2.5% for GMT/GMC ratio; Non-Inferiority -Two Independent Means – Two-sample T-tests for Non-Inferiority Assuming Equal Variance.

**Pass 2019: alpha = 2.5% for SCR difference; Non-inferiority: Proportions – Two independent Proportions – Non-Inferiority tests for Difference Between Two Proportions

For Flu D-QIV and mRNA-1273 booster vaccine: non-inferiority limit = 0.176 (=log10(1.5)), reference limit = 0.0413 (=log10(1.1)) for mRNA-1273 booster vaccine, reference limit = 0.017 (=log10(1.04)) for Flu D-QIV vaccine.

SCR Assumptions come from the US participants in the FLU D-QIV-008 study.

Participants who withdraw from the study will not be replaced.

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 (CIOMS) International Ethical Guidelines,
  - Applicable ICH Good Clinical Practice (GCP) Guidelines,
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted, to an IRB 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 IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants. Furthermore, any substantial amendments to the protocol may require regulatory authority approval before implementation per local legislation.
- PPD 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 annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB.
  - Notifying the IRB of SAE(s) or other significant safety findings as required by IRB procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB, and all other applicable local regulations.
- After reading the protocol, all principal investigators will sign the protocol signature page and send a copy of the signed page to PPD [see Investigator Agreement].

10.1.2. Financial disclosure

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

10.1.3. Informed consent process

The investigator or his/her representative must fully 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, prior to participation in the study.

The content of the informed consent form must meet the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB or study center.

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

Participants must be re-consented if a new version of the ICF(s) or an ICF addendum is released during their participation in the study.

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

Participants who are rescreened are required to sign a new ICF.

10.1.4. Data protection

Participants will be assigned a unique identifier by GSK/PPD. Any participant records or datasets transferred to GSK/PPD will contain only the identifier. Name and any other information which would identify the participant will not be transferred.

The participants must be informed that:

- His/her personal study-related data will be used by GSK in accordance with local data protection law.
- His/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by GSK/PPD, by appropriate IRB members, and by inspectors from regulatory authorities.

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

The participants must be notified about their rights regarding the use of their personal data in accordance with the data privacy section of the ICF.

10.1.5. Committees structure

Table 20 Study administrative structure

Function	Responsible organization
Clinical Supply Management, Quality Assurance Auditing	GSK
Laboratory Assessments	GSK
Randomization, Blinding, Unblinding	Cenduit
Study Operations Management, Medical Monitoring, Study Master File	PPD
Biostatistics, Medical Writing	PPD
Safety Review Team	GSK

Medical monitor

Refer to the Safety and Medical Management Plan.

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 applicable regulations/GSK policy. GSK will aim to register protocol summaries prior to study start and target results summaries submission within 12 months of primary/ study completion date. Where external regulations require earlier disclosure, GSK will follow those timelines.

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

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and provided reasonable access to statistical tables, figures, and relevant reports. GSK will also provide the investigator with the full summary of the study results. 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 study center only after completion of the full statistical analysis.

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

10.1.7. Data quality assurance

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

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

All participant data related to the study will be recorded on printed or eCRF unless transmitted to GSK/PPD or designee electronically (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

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

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

PPD is responsible for the data management of this study including quality checking of the source data (see Glossary of terms for the exact definition of source data).

Study monitors will perform ongoing source data verification to confirm that data entered in the eCRF by authorized site personnel are attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data must be traceable, not obscure the original entry, and be fully explained if necessary (e.g. via an audit trail). The safety and rights of participants must be protected, and the study conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Quality tolerance limits (QTLs) will be pre-defined in the Central Monitoring Plan to identify systematic issues that can impact participant safety and/or the reliability of study results. These pre-defined parameters will be monitored during the study. Important deviations from the QTLs and remedial actions taken will be summarized in the Clinical Study Report (CSR).

Study records and source documents pertaining to the conduct of this study, including signed ICFs, must be retained by the investigator for 25 years from issuance of the final CSR/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 GSK. No records may be transferred to another location or party without written notification to GSK.

10.1.8. Source documents

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

Data transcribed into the eCRF from source documents must be consistent with those source documents; any 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.

Definitions of what constitutes source data and documents can be found in the Glossary of terms.

10.1.9. Study and site start and closure

First act of recruitment

The first act of recruitment is the date of the first participant enrollment and is considered the study start date.

Study/Site termination

GSK reserves the right to close the study site or terminate the study at any time for any reason at its sole discretion, provided there is sufficient notice given to account for all participants safe exit from study.

Regular closure of study sites 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 enough notice in advance of the intended termination.

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, GSK/PPD's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development
- Total number of participants included earlier than expected

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

10.1.10. Publication policy

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

10.2. Appendix 2: Adverse events: definitions and procedures for recording, evaluating, follow-up, and reporting

10.2.1. Definition of an AE

An AE is any untoward medical occurrence (an unfavorable/unintended sign - including an abnormal laboratory finding), symptom, or disease (new or exacerbated) in a clinical study participant that is temporally associated with the study intervention. The AE may or may not be considered related to the study intervention.

10.2.1.1. 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 administration of the study intervention even though they may have been present before study start.
- Signs, symptoms, or the clinical sequelae of a suspected drug, disease or other interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either the study intervention or a concurrent medication.
- Signs or symptoms temporally associated with administration of the study intervention.
- Signs, symptoms that require medical attention (e.g., hospital stays, physician visits and emergency room visits)
- Significant failure of an expected pharmacologic or biological action.
- Pre- or post- intervention events that occur as a result of protocol-mandated procedures (e.g. invasive procedures, modification of participant's previous therapeutic regimen). Note this exception to AE definition for pre-intervention study-related events.
- An SAE related to a GlaxoSmithKline concomitant medicine/vaccine with onset any time after signing the ICF. Note this exception to AE definition for pre-intervention study-related events.

- 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 10.2.3. All other AEs will be recorded as UNSOLICITED AEs.

10.2.1.2. 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 before the first dose of study intervention (unless an untoward event with onset after signing the ICF and before first dose of study intervention that is either related to a study-procedure or is an SAE related to a GlaxoSmithKline concomitant medicine/vaccine). 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 before signing the informed consent) that did not worsen from baseline.
- Any clinically significant abnormal laboratory findings or other abnormal safety assessments associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

10.2.2. Definition of an 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 (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
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 must be exercised in deciding whether reporting is appropriate in other situations. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or require medical or surgical intervention to prevent one of the other outcomes listed in the above definition should 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; and convulsions that do not result in hospitalization.

In addition:

All suspected cases of anaphylaxis, in addition to being reported as an AESI, should be recorded as medically attended AEs and reported as an SAE, based on the criteria for a medically important event, unless the event meets other serious criteria. As an SAE, the event should be reported to PPD immediately and in all circumstances within 24 hours (per Section 10.2.10). The investigator will submit any updated anaphylaxis case data to PPD within 24 hours of it being available. For reporting purposes, a participant who displays signs or symptoms consistent with anaphylaxis (as follows) should be reported as a potential case of anaphylaxis. This is provided as general guidance for investigators and is based on the Brighton Collaboration case definition [Ruggeberg, 2007].

Anaphylaxis is an acute hypersensitivity reaction with multi-organ system involvement that can present as, or rapidly progress to, a severe life-threatening reaction. It may occur following exposure to allergens from a variety of sources.

Anaphylaxis is a clinical syndrome characterized by the following:

- Sudden onset AND
- Rapid progression of signs and symptoms AND
- Involves 2 or more organ systems, as follows:
  - Skin/mucosal: urticaria (hives), generalized erythema, angioedema, generalized pruritus with skin rash, generalized prickle sensation, and red and itchy eyes.

- Cardiovascular: measured hypotension, clinical diagnosis of uncompensated shock, loss of consciousness or decreased level of consciousness, and evidence of reduced peripheral circulation.
- Respiratory: bilateral wheeze (bronchospasm), difficulty breathing, stridor, upper airway swelling (lip, tongue, throat, uvula, or larynx), respiratory distress, persistent dry cough, hoarse voice, sensation of throat closure, sneezing, and rhinorrhea.
- Gastrointestinal: diarrhea, abdominal pain, nausea, and vomiting.

10.2.3. Solicited events

10.2.3.1. Solicited local adverse events

The following local AEs will be solicited at the time of the intervention:

Table 21 Solicited local adverse events

Pain
Redness
Swelling
Pruritus (for HZ/su vaccination only)
Axillary (underarm) swelling or tenderness ipsilateral to the site of mRNA-1273 booster vaccination

10.2.3.2. Solicited systemic events

The following systemic events will be solicited:

Table 22 Solicited systemic events

Fatigue
Myalgia
Headache
Shivering/chills
Fever
Gastrointestinal symptoms (nausea, vomiting, diarrhea and/or abdominal pain)
Arthralgia

Note: Participants will be instructed to measure and record the body temperature, preferably in the evening, using the temperature measuring device provided by GSK/PPD. The recommended route of temperature measurement will be the oral route. If additional temperature measurements are taken at other times of the day, participants will be instructed to record the highest temperature in the eDiary.

10.2.4. Unsolicited AEs

An unsolicited AE is an AE that was either not included in the list of solicited events using a Participant Diary or could be included in the list of solicited events but with an onset more than 7 days following administration of a study intervention. Unsolicited events must have been communicated by a participant who has signed the informed consent. Unsolicited AEs include both serious and non-serious AEs.

Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, or an emergency room visit, or visit to/by a health care provider). The participants will be instructed to notify the site as soon as possible to report medically attended events, as well as any events which, though not medically attended, are of participant's concern or which prevent the participant from normal daily activities. 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, perceived as a concern by the participant, nor prevented normal daily activities, will still be collected during an interview with the participants and by review of available medical records at the next visit.

10.2.5. Potential immune-mediated diseases

pIMDs include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune etiology. AEs that need to be recorded and reported as pIMDs include those listed in the Table 23.

The investigator must exercise his/her medical/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 23 List of potential immune-mediated diseases (pIMDs)

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

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) – Necrotising vasculitis (cutaneous or systemic) – Anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified) – Henoch-Schonlein purpura (IgA vasculitis) – Behcet's syndrome – Leukocytoclastic vasculitis	• Autoimmune haemolytic 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 • 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.

When there is enough evidence to make any of the above diagnoses, the AE must be reported as a pIMD. Symptoms, signs or conditions which might (or might not) lead to one of the above diagnoses, should be recorded and reported as AEs but not as a pIMD until the final or definitive diagnosis has been made, and alternative diagnoses eliminated or shown to be less likely. The reporting of pIMDs is restricted to study participants in the HZ/su and mRNA-1273 booster cohort.

10.2.6. Adverse events of special interest

The following AESIs (Table 24) are medical concepts that may be related to COVID-19 or are of interest in COVID-19 vaccine safety surveillance. Even if the events below occur in the setting of a COVID infection, the event should still be reported as an AESI if it is one of the medical concepts below.

Table 24 List of AESIs applicable to mRNA-1273 vaccine

Medical Concept	Additional Notes
Anosmia, Ageusia	• New onset COVID associated or idiopathic events without other etiology excluding congenital etiologies or trauma
Subacute thyroiditis	• Including but not limited to events of: atrophic thyroiditis, autoimmune thyroiditis, immune-mediated thyroiditis, silent thyroiditis, thyrotoxicosis and thyroiditis
Acute pancreatitis	• Including but not limited to events of: autoimmune pancreatitis, immune-mediated pancreatitis, ischemic pancreatitis, edematous pancreatitis, pancreatitis, acute pancreatitis, hemorrhagic pancreatitis, necrotizing pancreatitis, viral pancreatitis, and subacute pancreatitis • Excluding known etiologic causes of pancreatitis (alcohol, gallstones, trauma, recent invasive procedures)
Appendicitis	• Include any event of appendicitis
Rhabdomyolysis	• New onset rhabdomyolysis without known etiology such as excessive exercise or trauma
Acute respiratory distress syndrome (ARDS)	• Including but not limited to new events of ARDS and respiratory failure.
Coagulation disorders	• Including but not limited to thromboembolic and bleeding disorders, disseminated intravascular coagulation, pulmonary embolism, deep vein thrombosis
Acute cardiovascular injury	• Including but not limited to myocarditis, pericarditis, microangiopathy, coronary artery disease, arrhythmia, stress cardiomyopathy, heart failure, or acute myocardial infarction. • Myocarditis or pericarditis as defined per protocol Section 10.2.2, and follow reporting procedures in protocol Section 10.2.12
Acute kidney injury	• Include events with idiopathic or autoimmune etiologies • Exclude events with clear alternate etiology (trauma, infection, tumor, or iatrogenic causes such as medications or radiocontrast etc.) • Include all cases that meet the following criteria o Increase in serum creatinine by ≥ 0.3 mg/dl (≥26.5 umol/l) within 48 hours; o OR Increase in serum creatinine to ≥ 1.5 times baseline, known or presumed to have occurred within prior 7 days o OR Urine volume ≤0.5 ml/ kg/ hour for 6 hours
Acute liver injury	• Include events with idiopathic or autoimmune etiologies • Exclude events with clear alternate etiology (trauma, infection, tumor, etc.)

Medical Concept	Additional Notes
	• Include all cases that meet the following criteria o > 3-fold elevation above the upper normal limit for ALT or AST o OR > 2-fold elevation above the upper normal limit for total serum bilirubin or GGT or ALP
Dermatologic findings	• Chilblain-like lesions • Single organ cutaneous vasculitis • Erythema multiforme • Bullous rashes • Severe cutaneous adverse reactions including but not limited to: Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and fixed drug eruptions
Multisystem inflammatory disorders	• Multisystem inflammatory syndrome in adults (MIS-A) • Multisystem inflammatory syndrome in children (MIS-C) • Kawasaki's disease
Thrombocytopenia	• Platelet counts < 150 x10^9 • Including but not limited to immune thrombocytopenia, platelet production decreased, thrombocytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, or HELLP syndrome
Acute aseptic arthritis	• New onset aseptic arthritis without clear alternate etiology (e.g. gout, osteoarthritis, and trauma)
New onset of or worsening of neurologic disease	• Including but not limited to o Guillain-Barre Syndrome o Acute disseminated encephalomyelitis (ADEM) o Peripheral facial nerve palsy (Bell's palsy) o Transverse myelitis o Encephalitis/Encephalomyelitis o Aseptic meningitis o Febrile seizures o Generalized seizures/convulsions o Stroke (Hemorrhagic and non-hemorrhagic) o Narcolepsy
Anaphylaxis	• Anaphylaxis as defined per protocol Section 10.2.2. • Follow reporting procedures in protocol Section10.2.12
Other syndromes	• Fibromyalgia • Postural Orthostatic Tachycardia Syndrome • Chronic Fatigue Syndrome (Includes Myalgic encephalomyelitis and Post viral fatigue syndrome) • Myasthenia gravis

When there is enough evidence to make any of the above diagnoses, the AE must be reported as an AESI. Symptoms, signs or conditions which might (or might not) lead to one of the above diagnoses, should be recorded and reported as AEs but not as an AESI until the final or definitive diagnosis has been made, and alternative diagnoses eliminated or shown to be less likely.

Any case of suspected, probable, or confirmed myocarditis, pericarditis, or myopericarditis should be reported as an AESI, even if it does not meet criteria per the CDC case definition. The event should also be reported as an SAE if it meets any seriousness criterion listed in Section 10.2.2. The following CDC case definition [Gargano, 2021] is provided as guidance:

Acute Myocarditis:

PROBABLE CASE:

Presence of ≥1 new or worsening of the following clinical symptoms*:

- ***chest pain, pressure, or discomfort;***
- ***dyspnea, shortness of breath, or pain with breathing***
- ***palpitations***
- ***syncope***

AND

≥1 new finding of

- ***troponin level above upper limit of normal (any type of troponin)***
- ***abnormal electrocardiogram or rhythm monitoring findings consistent with myocarditis§***
- ***abnormal cardiac function or wall motion abnormalities on echocardiogram***
- ***cardiac magnetic resonance imaging (cMRI) findings consistent with myocarditis¶***

AND

- ***No other identifiable cause of the symptoms and findings***

CONFIRMED CASE:

Presence of ≥1 new or worsening of the following clinical symptoms*:

- ***chest pain, pressure, or discomfort;***
- ***dyspnea, shortness of breath, or pain with breathing***
- ***palpitations***
- ***syncope***

AND

≥1 new finding of

- ***histopathologic confirmation of myocarditis†***
- ***cMRI findings consistent with myocarditis¶ in the presence of troponin level above upper limit of normal (any type of troponin)***

AND

No other identifiable cause of the symptoms and findings

Acute Pericarditis**

Presence of ≥2 new or worsening of the following clinical features:

- ***acute chest pain††***
- ***pericardial rub on exam***
- ***new ST-elevation or PR-depression on electrocardiogram***
- ***new or worsening pericardial effusion on echocardiogram or MRI***

**** Persons who lack the listed symptoms but who meet other criteria may be classified as subclinical myocarditis (probable or confirmed).***

† Using the Dallas criteria [Aretz, 1987]. Autopsy cases may be classified as confirmed clinical myocarditis on the basis of meeting histopathologic criteria if no other identifiable cause.

§ To meet the electrocardiogram or rhythm monitoring criterion, a probable case must include at least one of i) ST-segment or T-wave abnormalities; ii) Paroxysmal or sustained atrial, supraventricular, or ventricular arrhythmias; or iii) atrioventricular nodal conduction delays or intraventricular conduction defects.

¶ Using either the original or the revised Lake Louise criteria [Ferreira, 2018].

***** [Adler, 2015].***

†† Typically described as pain made worse by lying down, deep inspiration, or cough, and relieved by sitting up or leaning forward, although other types of chest pain might occur.

Participants who meet criteria for both myocarditis and pericarditis may be described under myopericarditis.(Amended 21 September 2021)

All cases of myocarditis or pericarditis reported in an expedited manner as AESIs (and if a seriousness criterion is met, SAEs) may also be reviewed by an independent safety endpoint adjudication committee created by Moderna.

10.2.7. COVID-19 cases

COVID-19 cases identified during the study (as per standard of care) will be captured and reported using standard AE, medically-attended AE or SAE criteria, and routine procedures for recording, evaluation, follow-up, and reporting of AEs and SAEs should be followed in accordance with the time period set out in the protocol.

Diagnosis and categorization of COVID-19 cases for reporting purposes should be made in accordance with the following primary and secondary [Baden, 2021], and tertiary case definitions:

Primary Case Definition:

- The participant must have experienced at least TWO of the following systemic symptoms: fever (temperature ≥ 38ºC), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), OR
- The participant must have experienced at least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; AND
- The participant must have at least one nasopharyngeal (NP) swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by PCR

Secondary Case Definition:

Defined as the following systemic symptoms: fever (temperature ≥ 38ºC), or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle aches or body aches, headache, new loss of taste or smell, sore throat, nasal congestion or rhinorrhea, nausea or vomiting, or diarrhea AND a positive NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) for SARS-CoV-2 by PCR

Tertiary Case Definition:

Documented diagnosis of COVID-19 made by a health care provider and not meeting the primary or secondary case definitions.

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

In the absence of a diagnosis, abnormal laboratory findings assessments or other abnormal results 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 Sections 10.2.1 and 10.2.2).

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

10.2.9. Events or outcomes not qualifying as AEs or SAEs

10.2.9.1. Pregnancy

Female participants who become pregnant after the first study intervention dose must not receive subsequent doses of the study intervention but may continue other study procedures at the discretion of the investigator.

Female participants who become pregnant after administration of the study intervention may continue the study 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 Section 10.2.2 for definition of SAE.

10.2.10. Recording and follow-up of AEs, SAEs, AESIs, pIMDs, IMCs and pregnancies

The participants will be instructed to contact the investigator immediately should they experience any signs or symptoms they perceive as of concern.

When an AE/SAE occurs, it is the investigator's responsibility to review all documentation (e.g., hospital progress notes, laboratory and diagnostics reports) related to the event. The investigator will then record all relevant information regarding an AE/SAE on the eCRF. The investigator may not send photocopies of the participant's medical records to PPD instead of appropriately completing the eCRF.

There may be instances when copies of medical records for certain cases are requested by PPD. In this case, all participant identifiers will be blinded on copies of the medical records prior to submission to PPD.

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 instead of individual signs/symptoms.

An eDiary will be used in this study to capture solicited local or systemic events. The participant should be trained on how and when to complete the eDiary.

Anyone who measures local or systemic events and who will record the event in the eDiary should be trained on using the eDiary. This training must be documented in the participant's source record. Site staff will monitor eDiary compliance and the investigator will review and verify eDiary entries during discussions with the participant.

Any unreturned eDiary will be sought from the participant through telephone call(s) or any other convenient procedure.

Refer to the Monitoring Plan for more information regarding the use of eDiary.

10.2.10.1. Time period for collecting and recording AEs, SAEs, AESIs, pIMDs, and IMCs

All solicited events that occur during the 7 days (Day 1-Day 7) following administration of each dose of study intervention must be recorded into the eDiary, irrespective of intensity. All other AEs occurring within the timeframes for collecting and reporting noted in Section 8.3.1 should be recorded into the appropriate section of the eCRF, irrespective of their intensity or whether or not they are considered related to the study intervention.

10.2.10.2. Follow-up of AEs, SAEs, AESIs, pIMDs, and IMCs

After the initial AE/SAE/AESI/pIMD/and IMC, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, AESIs, pIMDs, and IMCs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.

Other non-serious AEs must be followed until the end of the study or until the participant is lost to follow-up.

10.2.10.2.1. Follow-up during the study

AEs 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 last visit/contact of the participant.

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

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

The investigator will provide any new or updated relevant information to PPD on a previously reported SAE/AESI/pIMD using an electronic Expedited Adverse Events Report. 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 SAE/AESI/pIMD as fully as possible.

10.2.10.2.3. Follow-up of pregnancies

The investigator is required to proactively follow each pregnancy at subsequent visits/contacts. 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 PPD using the electronic pregnancy report and the Expedited Adverse Events Report if applicable. Generally, the follow-up period does not need to be longer than 6 to 8 weeks after the estimated date of delivery.

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

Furthermore, if the investigator becomes aware of any SAE occurring as a result of a post-study pregnancy AND it is considered by the investigator to be reasonably related to the study intervention, he/she must report this information to PPD as described in the Section 10.2.12.

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

When additional SAE, AESI, pIMD or pregnancy information is received after write access to the participant's eCRF is removed, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be faxed to PPD within the defined reporting timeframes specified in the Table 15.

10.2.11. Assessment of intensity and toxicity

10.2.11.1. Assessment of intensity

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

Table 25 Intensity scales for AEs

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.

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.

The maximum intensity of injection administration site redness/swelling and fever will be graded as follows:

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.

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.

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.

10.2.11.2. Assessment of causality

The investigator must assess the relationship between study intervention and the occurrence of each unsolicited AE/SAE using clinical judgement. Where several different interventions were administered, the investigator should specify, when possible, if the unsolicited AE/SAE could be causally related to a specific intervention. When a causal relationship to a specific study intervention cannot be determined, the investigator should indicate the unsolicited AE/SAE to be related to all interventions.

Alternative possible causes, such as the natural history of underlying disease, concomitant therapy, other risk factors, and the temporal relationship of the event to the study intervention will be considered and investigated. The investigator will also consult the IB and/or SmPC and/or Prescribing Information for marketed products to assist in making 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 intervention?*

YES: There is a reasonable possibility that the study intervention contributed to the AE.

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

If an event meets the criteria to be determined 'serious' (see Section 10.2.2), 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 study intervention, if applicable.
- An error in study intervention 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 PPD. However, it is very important to record an assessment of causality for every event before submitting the Expedited Adverse Events Report to PPD.

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.

10.2.11.3. Medically attended visits

For each solicited and unsolicited AE 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/Expedited Adverse Events Report as applicable.

10.2.11.4. 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).

10.2.12. Reporting of SAEs, AESIs, pIMDs, and pregnancies

10.2.12.1. Events requiring expedited reporting to PPD

Once an investigator becomes aware that a participant has experienced an SAE/AESI/pIMD/pregnancy, the investigator (or designee) must complete information in the electronic Expedited Adverse Events Report/electronic pregnancy report (as applicable) WITHIN 24 HOURS, even if the investigator does not have complete information on the SAE/AESI/pIMD/pregnancy. It must be completed as thoroughly as possible, with all available details of the event.

The SAE/AESI/pIMD/pregnancy report must be updated WITHIN 24 HOURS of the receipt of updated information on the SAE/AESI/pIMD/pregnancy. The investigator will always provide an assessment of causality at the time of the initial SAE/AESI/pIMD report.

Refer to the Table 14 for the details on timeframes for reporting of SAEs/AESIs/pIMDs/pregnancies. Refer to Section 10.2.12.2 for information on back-up systems in case the electronic reporting system does not work.

The investigator will be required to confirm the review of SAE causality in the electronic Expedited Adverse Event Report within 72 hours of submission of the SAE.

SAE/AESI/pIMD/pregnancy reporting to PPD via an electronic data capture Tool

- The primary mechanism for reporting an SAE/AESI/pIMD/pregnancy to PPD will be the electronic Data Capture (EDC) Tool.
- If the EDC is unavailable for more than 24 hours, then the study center will use the paper Expedited AE Report or pregnancy report (as applicable).
- The study center staff will enter the SAE/AESI/pIMD/pregnancy data into the EDC as soon as it becomes available.
- After the study is completed at a given site, the EDC will be taken offline to prevent the entry of new data or changes to existing data.
- If a study center receives a report of a new SAE from a participant or receives updated data on a previously reported SAE after the EDC has been taken offline, then the study center can report this information on a paper Expedited AE Report (see the next section).

10.2.12.2. Back-up system in case the electronic reporting system does not work

If the electronic reporting system does not work, the investigator (or designee) must fax a completed, dated and signed paper Expedited Adverse Events Report or pregnancy report (as applicable) to the study contact for reporting SAEs/AESIs/pIMDs/pregnancies (refer to Section 8.3.3.1) within 24 hours of becoming aware of the event.

Investigator (or designee) must complete the electronic Expedited Adverse Events Report or pregnancy report (as applicable) within 24 hours after the electronic reporting system is working again. The information reported through the electronic reporting system will be considered valid for regulatory reporting purposes.

10.3. Appendix 3: Contraceptive guidance and collection of pregnancy information

10.3.1. Definitions

10.3.1.1. Woman of childbearing potential (WOCBP)

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

10.3.1.1.1. Women not considered as women of childbearing potential

- **Premenarchal***

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

  Additional evaluation should be considered if a participant's fertility status is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention.

  **Note: If the childbearing potential changes after start of the study (e.g., a premenarchal female participant experiences menarche) or the risk of pregnancy changes (e.g., a female participant who is not heterosexually active becomes active), the participant must discuss this with the investigator, who should determine a highly effective method of contraception. If reproductive status is questionable, additional evaluation should be considered.*

- Premenopausal female with ONE of the following:
  - Documented total hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
  - Current bilateral tubal ligation or occlusion

  Note: Documentation can come from the study center 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 (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

- Females on HRT and whose menopausal status is in doubt will be required to use a non-hormonal, highly effective contraception method if they wish to continue their HRT during the study. Alternatively, confirmation of post-menopausal status before study enrolment should be established.

10.3.2. Contraception guidance

- Female participants of childbearing potential are eligible to participate if they agree to use a highly effective contraceptive method consistently and correctly according to the methods listed in GSK's list of highly effective contraceptive methods (Table 26).

Table 26 Highly effective contraceptive methods

Highly Effective Contraceptive Methods That Are User Dependent *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 • Oral
Highly Effective Methods That Are User Independent*
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • 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 WOCBP, 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 study center 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.)*

Female participants must practice adequate contraception for 30 days prior to vaccination, have a negative pregnancy test on the day of vaccination, and agree to continue adequate contraception during the entire intervention period and for 2 months after completion of the vaccination series.

10.3.3. Collection of pregnancy information

10.3.3.1. Female participants who become pregnant

Refer to Sections 8.3.1, 8.3.2, 10.2.9.1, 10.2.10, and 10.2.10.2 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.

10.4. Appendix 4: Definition of medical device AE, adverse device effect (ADE), serious adverse device effect (SADE) and unanticipated SADE (USADE)

10.4.1. Definition of medical device AE and adverse device effect (ADE)

- Medical device AE is any untoward medical occurrence, in a clinical study participant, users, or other persons, temporally associated with the use of study intervention whether considered related to a medical device or not. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medical device. This definition includes events related to the medical device or comparator and events related to the procedures involved.
- An adverse device effect (ADE) is an AE related to the use of a medical device. This definition includes any AE resulting from:
  - Insufficient or inadequate instructions for use (i.e. user error), or
  - Any malfunction of a medical device, or
  - Intentional misuse of the medical device.

10.4.2. Definitions of a medical device SAE, serious adverse device effect, and unexpected serious adverse device effect

A Medical Device SAE is any SAE that:
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: – A life-threatening illness or injury. The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. – A permanent impairment of a body structure or a body function. – Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. – Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
c. Led to fetal distress, fetal death or a congenital abnormality or birth defect
d. Is a suspected transmission of any infectious agent via a medicinal product

A Serious Adverse Device Effect (SADE) is:
• A SADE is defined as an ADE that has resulted in any of the consequences characteristic of an SAE. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
An Unanticipated SADE (USADE) is:
• An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is a SADE that by its nature, incidence, severity or outcome has not been identified in the current version of the IB.

10.4.3. Recording and reporting of medical device AE, ADEs, SADEs and USADE

- The primary mechanism for reporting a medical device related event to PPD will be the EDC Tool.
- If the EDC is unavailable for more than 24 hours or if a device eCRF is not available, then the study center will fax the paper "Medical device or combination product with device deficiency/incident report form" to PPD.
- In rare circumstances and in the absence of Fax equipment, notification by phone is acceptable with a copy of "Medical device or combination product with device deficiency/incident report form" sent by overnight mail or courier service.
- The study center staff will enter the medical device related event data into the EDC as soon as it become available.
- Any device deficiencies must be reported to PPD within 24 hours after the investigator determines that the event meets the definition of a device deficiency.
- Contact for reporting can be found in Section 8.3.3.1
- PPD will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs as required by national regulations.

10.5. Appendix 5: Abbreviations and glossary of terms

10.5.1. List of abbreviations

AE	adverse event
AESI	adverse event of special interest
AESIs	adverse events of special interest
ANCOVA	analysis of covariance
AS	adjuvant system
$AS01_B$	adjuvant System 01B
CBER	Center for Biologics Evaluation and Research
CD4	cluster of differentiation 4
CDC	Center for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
cMRI	cardiac magnetic resonance imaging
COVID-19	coronavirus disease 2019
CSR	clinical study report
DLP	data lock point
eCRF	electronic case report form
EDC	electronic data capture
ELISA	enzyme linked immunosorbent assay
EUA	emergency use authorization
FDA	U.S. Food and Drug Administration
Flu D-QIV	quadrivalent seasonal influenza vaccine
FluD-QIVCoAd	group receiving the mRNA-1273 booster dose co-administered with the Flu D-QIV dose
FluD-QIVSeq	group receiving the mRNA-1273 booster dose followed by the Flu D-QIV dose
GBS	Guillain-Barré Syndrome
gE	glycoprotein E
GMC	geometric mean concentration
GMT	geometric mean titer
HA	hemagglutinin
HI	hemagglutinin inhibition

HRT	hormone replacement therapy
HZ	herpes zoster
HZ/su	Herpes Zoster subunit vaccine
HZ/suCoAd	group receiving the mRNA-1273 booster dose co-administered with first dose of HZ/su
HZ/suSeq	group receiving the mRNA-1273 booster dose followed by the first dose of HZ/su
IB	Investigator's Brochure
ICH	International Council for Harmonization
ID	identification number
IgG	immunoglobulin G
IMC	intercurrent medical condition
IRB	Institutional Review Board
IRT	Interactive Response Tool
LNP	lipid nanoparticle
LPLV/LSLV	last participant last visit/last subject last visit
MedDRA	Medical Dictionary for Regulatory Activities
MGI	mean geometric increase
MM	Medical Monitor
MPL	3-O-desacyl-4'-monophosphoryl lipid A
mRNA	messenger ribonucleic acid
mRNA-1273	mRNA-based vaccine against COVID-19
N	nucleocapsid
NA	neutralizing antibody
NP	nasopharyngeal
OA	older adults
PCR	polymerase chain reaction
PHN	postherpetic neuralgia
pIMD	potential immune mediated disease
PPS	per protocol set
PT	preferred term
q.s	*quantum satis*
QS-21	*Quillaja saponaria* Molina, fraction 21
QTL	quality tolerance limit

RBD	receptor binding domain
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SCR	seroconversion rate
SD	Standard Deviation
SoA	schedule of activities
SOC	system organ class
SPR	seroprotection rate
S-protein	spike protein
SRT	safety review team
su	subunit
UL	upper limit
VRR	vaccine response rate
VZV	varicella zoster virus
WHO	World Health Organization
YOA	years of age

10.5.2. 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 study 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 study, 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 open-label study, no blind is used. Both the investigator and the participant know the identity of the intervention assigned.
Caregiver:	A caregiver is someone who • lives in the close surroundings of a participant and has a continuous caring role or • has substantial periods of contact with a participant and is engaged in his/her daily health care (e.g., a relative of the participant). In the context of a clinical study, a caregiver could include an individual appointed to oversee and support the participant's compliance with protocol specified procedures.
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.
Combination product:	Combination product comprises any combination of • drug • device • biological product Each drug, device, and biological product included in a combination product is a constituent part.
Eligible:	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Enrollment:	The process of registering a participant into a clinical study by assigning participant identification number after signing the ICF.
Enrolled participant:	"Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process.
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 studies.

Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per protocol analysis.
Immunological correlate of protection:	A correlate of risk that has been validated to predict a certain level of protection from the targeted endpoint.
Intercurrent medical condition	A condition that has the capability of altering the immune response to the study intervention or is confirmed to have an alteration of the participant's initial immune status.
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.
Invasive medical device:	A device which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body
Investigational vaccine/product:	A pharmaceutical form of an active ingredient being tested in a clinical study, 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.
Investigator:	A person responsible for the conduct of the clinical study at a study center. If a study is conducted by a team of individuals at a study center, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate study-related duties and functions conducted at the study center to qualified individual or party to perform those study-related duties and functions.
Interactive Voice/Web Response System:	The software that enables the randomizing of participants into clinical trials and allocation of the study product to them in a blinded fashion. This technology allows study centers to interact with a database by pressing keypad buttons on a phone and following voice or online prompts in order to enter in information.
Medical device deficiency:	A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors and information supplied by the manufacturer.

Medical Monitor	PPD's delegate providing significant scientific contribution to the conduct of the study. The terms Medical Officer, Medical Advisor are also used in some settings.
Medically attended AEs:	Symptoms or illnesses requiring hospitalization, or emergency room visit, or visit to/by a health care provider.
Participant:	Term used throughout the protocol to denote an individual who has been contacted to participate or participates in the clinical study, as a recipient of the study intervention (vaccine(s)/product(s)/control). Synonym: subject
Participant ID:	A unique identification number assigned to each participant who consents to participate in the study.
Protocol amendment:	The ICH defines a protocol amendment as "A written description of a change(s) to or formal clarification of a protocol." GSK further details this to include a change to an approved protocol that affects the safety of participants, scope of the investigation, study design, or scientific integrity of the study.
Randomization:	Process of random attribution of intervention to participants to reduce selection bias.
Safety Review Team:	This team lead by safety comprises of core representatives from GSK global safety, clinical, epidemiology, regulatory, and statistics departments, who are also part of the study team and representatives from Moderna. For this study, this team is responsible for reviewing the safety data.
Solicited events:	Events to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the participant or an observer during a specified follow-up period following study intervention administration.
Source data:	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. 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 study).
Study/Center Monitor:	An individual assigned by GSK/PPD (see the study administrative structure in Table 20) and responsible for assuring proper conduct of clinical studies at 1 or more study centers. The terms Clinical Research Monitor and Clinical Research Associate are used in some settings.
Study intervention:	Any investigational or marketed product(s) or placebo intended to be administered to a participant during the study.
Treatment number:	A number identifying intervention given to a participant, according to intervention allocation.
Unsolicited events:	Any AE reported in addition to those solicited during the clinical study. Also, any "solicited" symptom with onset outside of the specified period of follow-up for solicited symptoms will be reported as an unsolicited AE.

10.6. Appendix 6: Protocol Amendment Summary of Changes

10.6.1. Document history

Document	Date
Protocol Final	3 August 2021
Amendment 1 Final	21 September 2021

Amendment 1

Overall Rationale for the Amendment:

This amendment is intended to modify the dose of each mRNA-1273 booster injection to 50 mcg from 100 mcg.

10.6.2. List of main changes in the protocol and their rationale

Section # and Name	Description of Change	Brief Rationale
2.2 Background	Moderna ***has been*** ~~is~~ evaluating the use of ***50 µg (half dose) or*** 100 µg ***(full dose)*** of mRNA-1273 as a booster vaccine in participants previously vaccinated with 2 doses of 100 µg mRNA-1273 as a primary series. ***Available data indicates that boosting with half dose of the prototype mRNA-1273 has acceptable safety profile and induces robust neutralization titers against the Wuhan strain and variant viruses tested in all participants [***Wu***, 2021b]. It is however unclear if the half dose will sufficiently boost the immune response against other variants that***	***Background for consideration of the 50 µg dose of the mRNA-1273 vaccine.***

Section # and Name	Description of Change	Brief Rationale
	are expected to emerge as the pandemic continues to evolve. Additional trials are underway to assess the safety and immunogenicity of different dose levels of the booster vaccines e.g.100 µg of mRNA-1273 (clinicaltrials.gov: NCT04889209), as well as newly developed variant-specific vaccines (clinicaltrials.gov: NCT04927065). ***As of September 14th, 2021, the half dose (50 µg) mRNA-1273 booster is one of the COVID-19 booster vaccines recommended in the UK, to be administered at least 6 months after the primary series for certain populations at higher risk of severe COVID-19 disease. [JCVI 2021] The half dose mRNA-1273 booster is under evaluation by other health agencies such as the European Medicines Agency and the US Food and Drug Administration. (Amended 21 September 2021)***	
4.2 Scientific Rationale	As of summer, 2021, vaccines against COVID-19 in people ages 12 years and older have become an essential part of healthcare procedures to control the COVID-19 pandemic. ***With the emergence and spread of the SARS-CoV-2 virus variants that may not be sufficiently controlled by the primary vaccinations,*** periodic administration of booster COVID-19 vaccines after primary vaccination ***is either already recommended for specific populations or is under consideration by various health agencies*** ~~may soon become necessary~~.	***Amended to reflect the current regulatory environment.***
4.3 Justification of dose.	Moderna's mRNA-1273 vaccine is authorized for use in the U.S in adults 18 YOA and older under an EUA by the FDA and as a primary series of two 100 µg doses administered 1 month apart. Doses of 100 µg and 50 µg of the same vaccine are being investigated as a potential booster dose to be administered following the primary series. Preliminary results have shown that a 50 µg mRNA-1273 booster dose at least 6 months following the primary series substantially increases neutralizing antibodies against the wildtype SARS-CoV-2 virus and other tested variants, with a safety profile consistent with the known profile in earlier clinical trials [Wu, 2021b]. Currently, in light of the evolving emergence of SARS-CoV-2 variants, it is anticipated that a booster vaccine ***may be*** ~~is~~ needed. ***The current available data suggests that 50*** µg ***(half dose)*** of mRNA-1273 may be ***sufficient to boost immune response against the existing variants. This half dose is now recommended for boosting in the UK for certain populations at high risk for severe disease, to be administered 6 months post the primary series. This dose is also under review by other***	***Justification of Moderna mRNA 1273 booster dose reduction from 100 µg to 50 µg.***

Section # and Name	Description of Change	Brief Rationale
	health agencies ~~most effective.~~ As a result, ***50*** µg of mRNA-1273 will be used in this study. ***To note: If a different dose of mRNA-1273 is approved and recommended for use as a booster in the US while the study is ongoing, the dose of mRNA-1273 booster in the study will be adjusted in the HZ/su and mRNA-1273 booster cohort to the approved dose. The sample size in this cohort will also be adjusted accordingly to ensure sufficient power to achieve the corresponding primary objectives with the adjusted dose. The data generated with the 50 µg of mRNA-1273 booster will then be informative and add to the body of safety and immunogenicity data at this dose level. (Amended 21 September 2021)***	
6.3.2 Randomization to study intervention	The stratification by age will be set to **target** ~~ensure~~ a minimum of 75 participants in the ≥ 65 YOA stratum in each group. ~~This minimum number of participants will provide sufficient data for analysis of CBER criteria for SPR and SCR by age category~~.	***Due to a later than anticipated start to the study, potential elderly participants may have mostly already received their seasonal influenza vaccines and no longer be eligible***.
9.5.1 Sample size for HZ/su and mRNA-1273 study cohort	***Note: If the dose of mRNA-1273 booster is adjusted while the study is ongoing, the sample size will be compensated in this cohort to ensure that there are enough evaluable participants in each group.***	***Unlike seasonal influenza unpredictability, we would still be able to continue the study and re-estimate sample size requirements for the HZ/su and mRNA-1273 study cohort and make details explicit in a subsequent protocol amendment***.
10.2.6 Adverse Events of Special Interest	***Any case of suspected, probable, or confirmed myocarditis, pericarditis, or myopericarditis should be reported as an AESI, even if it does not meet criteria per the CDC case definition. The event should also be reported as an SAE if it meets any seriousness criterion listed in Section 10.2.2.***~~All cases of myocarditis or pericarditis with onset less than 7 days following mRNA-1273 administration, in addition to being reported as an AESI, should be recorded as causally related SAEs, based on the criteria for a medically important event, unless the event meets other serious criteria. As an SAE, the event should be reported to PPD immediately and in all circumstances within 24 hours (per Section 10.2.12). The investigator will submit any updated myocarditis or pericarditis case data to PPD within 24 hours of it being available. For reporting purposes, to ensure consistent case ascertainment, t~~ **The following CDC working case definition of myocarditis or pericarditis [Gargano, 2021] is provided as guidance.** ~~should be used~~:	***Text on AESI reporting of myocarditis and pericarditis made consistent with text in other Moderna protocols submitted to IND in past; thereby, also requiring moving from SAE section to AESI section in protocol***.

11. REFERENCES

Adler Y, Charron P, Imazio M, et al. ESC Guidelines for the diagnosis and management of pericardial diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC)Endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2015 Nov 7;36(42):2921-2964.

Aretz HT, Billingham ME, Edwards WD, et al. Myocarditis. A histopathologic definition and classification. *Am J Cardiovasc Pathol* 1987; 1:3–14

Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med*. 2021 Feb 4;384(5):403-416.

Bastidas A, de la Serna J, El Idrissi M, et al. Effect of Recombinant Zoster Vaccine on Incidence of Herpes Zoster After Autologous Stem Cell Transplantation. *JAMA*. 2019; 322(2): 123-133. (ZOSTER-002)

Brydak LB, Roszkowska-Blaim M, Machala M, Leszczyńska B, Sieniawska M. "Antibody response to influenza immunization in two consecutive epidemic seasons in patients with renal diseases" *Vaccine* 2000 Aug 1;18(28):3280-6.

Cao X. COVID-19: immunopathology and its implications for therapy. *Nat Rev Immunol.* 2020 May;20(5):269-70.

Centers for Disease Control and Prevention (CDC). Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR*. 2010;59(RR-8):1-62.

Centers for Disease Control and Prevention (CDC). Shingles (Herpes Zoster). Vaccination 2019. https://www.cdc.gov/shingles/vaccination.html. Accessed on 29 June 2021

Centers for Disease Control and Prevention (CDC). Who Needs a Flu Vaccine and When 2021a. https://www.cdc.gov/flu/prevent/vaccinations.htm. Accessed on 24 July 2021

Centers for Disease Control and Prevention (CDC). COVID-19 Stats: COVID-19 Incidence, by Age Group — United States, March 1–November 14, 2020. *MMWR Morb Mortal Wkly Rep* 2021b;69:1664.

Centers for Disease Control and Prevention (CDC) Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Authorized in the United States 2021c. https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html. Accessed on 14 July 2021

Chin J, Magoffin RL, Shearer LA, Schieble JH, Lennette EH. Field evaluation of a respiratory syncytial virus vaccine and a trivalent parainfluenza virus vaccine in a pediatric population. *Am J Epidemiol*. 1969 Apr;89(4):449-63.

Chu L, McPhee R, Huang W, et al. A preliminary report of a randomized controlled phase 2 trial of the safety and immunogenicity of mRNA-1273 SARS-CoV-2 vaccine. Vaccine. 2021 May 12;39(20):2791-2799.

Cunningham AL, Lal H, Kovac M, et al. Efficacy of the Herpes Zoster Subunit Vaccine in Adults 70 Years of Age or Older. *N Engl J Med*. 2016;375(11):1019-32. (ZOSTER -006, ZOSTER-022)

Cunningham AL, Heineman TC, Lal H, et al. Immune Responses to a Recombinant Glycoprotein E Herpes Zoster Vaccine in Adults Aged 50 Years or Older. *J Infect Dis.* 2018; 217(11): 1750-60. (ZOSTER-006, ZOSTER-022)

Dagnew AF, Ilhan O, Lee WS, et al. Immunogenicity and safety of the adjuvanted recombinant zoster vaccine in adults with haematological malignancies: a phase 3, randomised, clinical trial and post-hoc efficacy analysis. *Lancet Infect Dis.* 2019 ;19(9) : 988-1000. (ZOSTER-039)

Diez-Domingo J, Parikh R, Bhavsar AB, et al. Can COVID-19 Increase the Risk of Herpes Zoster? A Narrative Review. Dermatol Ther (Heidelb). 2021 May 17:1–8. Doi: 10.1007/s13555-021-00549-1.

Doria-Rose N, Suthar MS, Makowski M, et al. Antibody Persistence through 6 Months after the Second Dose of mRNA-1273 Vaccine for Covid-19. *N Engl J Med*. 2021 Jun 10;384(23):2259-2261. doi: 10.1056/NEJMc2103916. Epub 2021 Apr 6. PMID: 33822494.

Dougherty K, Mannell M, Naqvi O, et al. SARS-CoV-2 B.1.617.2 (Delta) Variant COVID-19 Outbreak Associated with a Gymnastics Facility — Oklahoma, April–May 2021. MMWR Morb Mortal Wkly Rep. ePub: 9 July 2021

Elsaie ML, Nada HA. Herpes zoster (shingles) complicating the course of COVID19 infection. J Dermatolog Treat. 2020 Oct 12:1-3.

Ferreira VM, Schulz-Menger J, Holmvang G, et al. Cardiovascular Magnetic Resonance in Nonischemic Myocardial Inflammation: Expert Recommendations. *J Am Coll Cardiol*. 2018 Dec 18;72(24):3158-3176.

Fontanet A, Autran B, Lina B, et al. SARS-CoV-2 variants and ending the COVID-19 pandemic. The Lancet, 2021, 397 (10278): 952-954

Fulginiti VA, Kempe CH. Killed-measles-virus vaccine. *Lancet*. 1967 Aug 26;2(7513):468.

Gargano JW, Wallace M, Hadler SC, et al. Use of mRNA COVID-19 Vaccine After Reports of Myocarditis Among Vaccine Recipients: Update from the Advisory Committee on Immunization Practices — United States, June 2021. MMWR Morb Mortal Wkly Rep 2021;70:977–982.

Greco A, Gallo A, Fusconi M, Marinelli C, Macri GF, deVincentis M. Bell's Palsy and autoimmunity. Autoimmunity Reviews. 2012;12:323-8.

Haber P, Sejvar J, Mikaeloff Y, DeStefano F. Vaccines and Guillain-Barré syndrome. Drug Safety. 2009;32(4):309-23.

Hannoun C, Megas F, Piercy J. Immunogenicity and protective efficacy of influenza vaccination. *Virus Res* 2004; 103:133-138.

Hobson D, Curry RL, Beare AS, et al., The role of serum haemagglutination-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses. *J Hyg Cam* 1972; 70:767-777.

Hu B, Guo H, Zhou P, Shi Z-L. Characteristics of SARS- CoV-2 and COVID-19. Nat Rev Microbiol 2020.

Jackson LA, Anderson EJ, Rouphael NG. An mRNA Vaccine against SARS-CoV-2 - Preliminary Report. N Engl J Med. 2020 Nov 12;383(20):1920-1931.

JCVI statement regarding a COVID-19 booster vaccine programme for winter 2021 to 2022 - GOV.UK (www.gov.uk). Accessed 15 Sept 2021.

Johnson R. Herpes zoster and postherpetic neuralgia. *Expert Rev Vaccines.* 2010;9(3 Suppl):21-6

Lal H, Cunningham AL, Godeaux O, et al. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. *N Engl J Med*. 2015;372(22):2087-96 (ZOSTER-006).

Lee C, Cotter D, Basa J, Greenberg HL. Post COVID-19 Vaccine Related Shingles Cases seen at the Las Vegas Dermatology Clinic and sent to us via Social Media. *J Cosmet Dermatol*. 2021 May 15. Doi: 10.1111/jocd.14210. Epub ahead of print. PMID : 33991162.

López-Fauqued M, Campora L, Delannois F, et al. Safety profile of the adjuvanted recombinant zoster vaccine: Pooled analysis of two large randomised phase 3 trials. Vaccine. 2019;37(18):2482-93. (ZOSTER-006, ZOSTER-022)

López-Fauqued, M., Co-van der Mee, M., Bastidas, A. et al. Safety Profile of the Adjuvanted Recombinant Zoster Vaccine in Immunocompromised Populations: An Overview of Six Trials. Drug Saf 44, 811–823 (2021).

Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med. 1985;4:213-226.

Mustafa SS. Anaphylaxis. [updated 14 February 2012, accessed 18 July 2012] Available at Medscape website: emedicine.medscape.com/article/135065-overview.

Pegu A, O'Connell S, Schmidt SD, et al. Durability of mRNA-1273-induced antibodies against SARS-CoV-2 variants. bioRxiv [Preprint]. 2021 May 16:2021.05.13.444010.

Rimmelzwaan GF, McElhaney JE; Correlates of protection: novel generations of influenza vaccines. Vaccine, 2008; 26 (Suppl 4):D41-D44.

Ruggeberg JU, Gold MS, Bayas JM, et al. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2007;25:5675-84.

Thomas SJ, Yoon IK. A review of Dengvaxia: development to deployment. Hum Vaccin Immunother. 2019;15(10):2295-2314.

Tufan A, Avanoğlu Güler A, Matucci-Cerinic M. COVID-19, immune system response, hyperinflammation and repurposing antirheumatic drugs. *Turk J Med Sci* 2020;50:620-32.

U.S. Food and Drug Administration (FDA). Combination Product Definition Combination Product Types. Content current as of 15 February 2018. https://www.fda.gov/combination-products/about-combination-products/combination-product-definition-combination-product-types. Accessed on 16 June 2021

Wang B, Guo S, Yao Y, Li Y, Zhang G. Dermatologists may need to pay more attention to herpes zoster during the pandemic of COVID-19, *Infectious Diseases* 2020;52(12):917-8. https://doi.org/10.1080/23744235.2020.1797158.

World Health Organization (WHO) Dengue vaccines: WHO position paper. who_pp_dengue_2018_summary.pdf. Accessed 14 July 2021.

World Health Organization (WHO). Coronavirus disease 2019 Dashboard. https://covid19.who.int/. Accessed on 27 July 2021.

World Health Organization (WHO). Influenza. WHO recommendations on the composition of influenza virus vaccines. http://www.who.int/influenza/vaccines/virus/recommendations/en/. Accessed on 08 June 2021

Wu K, Werner AP, Moliva JI, et al. mRNA-1273 vaccine induces neutralizing antibodies against spike mutants from global SARS-CoV-2 variants. bioRxiv [Preprint]. 2021a Jan 25:2021.01.25.427948.

Wu K, Werner AP, Koch M, et al. Serum Neutralizing Activity Elicited by mRNA-1273 Vaccine. *N Engl J Med*. 2021b;384(15):1468-1470.

Yuki N, Hartung HP. Guillain-Barré syndrome. *N Engl J Med*. 2012;366(24):2294-304.

Zent O, Arras-Reiter C, Broeker M, Hennig R. Immediate allergic reactions after vaccinations--a post-marketing surveillance review. *Eur J Pediatr*. 2002 Jan;161(1):21-5.

Signature Page for 217670 TMF-14013230 v1.0

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 21-Sep-2021 18:31:40 GMT+0000

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 21-Sep-2021 19:51:40 GMT+0000

Signature Page for TMF-14013230 v1.0