GlaxoSmithKline Biologicals SA (GSK)

217670 (ZOSTER-091)

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

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Statistical Analysis Plan

Amendment 1.0

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Amendment Summary of Changes

This document is an amendment to statistical analysis plan version 1 dated December 3, 2021. A table of changes is presented below.

Revision Chronology:	
Version	**Date**
Original	03DEC2021
Amendment No. 1	Refer to Last Signature
Updates include: • Updates to the interim analysis (IA) details due to immunogenicity data not being available at the time of the IA. • Additional non-evaluable rates provided in an appendix to demonstrate the power for situations where the non-evaluable rate is >10%. • Clarifications that the PPS is evaluated per vaccine (HZ/su, Flu D-QIV, and mRNA-1273) • Additional summaries added for new subgroups safety, reactogenicity and immunogenicty endpoints and for the Exposed set in immunogenicity endpoints. • Clarifications added regarding actual data and analysis details that deviated from protocol. • Other minor edits for clarification.	

List of Abbreviations

AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CBER	Center for Biologics Evaluation and Research
CI	Confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
DBF	database freeze
ECG	electrocardiogram
FAS	full analysis set
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 DQIV dose
gE	glycoprotein E
GI	gastrointestinal
GMC	geometric mean concentration
GMT	geometric mean titer
HI	hemagglutinin inhibition
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
IA	interim analysis
IMC	intercurrent medical condition
IRT	interactive response tool
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MGI	mean geometric increase
MPL	3-O-desacyl-4'-monophosphoryl lipid A
mRNA	messenger ribonucleic acid
mRNA-1273	mRNA-based vaccine against COVID-19
PCR	Polymerase chain reaction
pIMD	potential immune mediated disease
PPS	per protocol set
PT	preferred term
RBD	Receptor binding domain
SAE	serious adverse event

SAP	statistical analysis plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SOC	system organ class
SCR	seroconversion rate
S-protein	spike protein
SPR	seroprotection rate
SRT	safety review team
su	subunit
ULOQ	Upper limit of quantification
VRR	vaccine response rate
VZV	varicella zoster virus
WHO	World Health Organization
YOA	years of age

1. Introduction

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).

This statistical analysis plan (SAP) is developed to provide the details of the planned statistical methodology for both the interim analysis and final analysis (used for the preparation of final study report after database lock). It is based upon the final protocol amendment version date 21 September 2021. The SAP is finalized prior to the interim analysis (IA) start. The SAP amendment is finalized prior to final database lock. Major changes in the analysis that are made after database lock will be documented in the Clinical Study Report along with the rationale and other details.

2. Objectives

2.1. Primary Objective and Endpoints

Objectives	Endpoints
• 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).

2.2. Secondary Objectives and Endpoints

Objectives	Endpoints
Secondary – Immunogenicity	
• 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% confidence interval (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).

Objectives	Endpoints
Secondary – Immunogenicity	
• 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 seroprotection rate (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). • 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 years of age [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
Secondary – Safety/Reactogenicity	
• 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**: o 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. o 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)**: o Number and percentage of participants reporting SAEs from first dose up to 30 days post-last dose within each group. o 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:** o Number and percentage of participants reporting of pIMDs from first dose up to 30 days post-last dose within each group. o Number and percentage of participants reporting pIMDs from first dose to study end. • **Adverse events of special interest (AESIs):** o Number and percentage of participants reporting AESIs from first dose up to 30 days post-last dose within each group. o 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**: Number and percentage of participants meeting case definitions of COVID-19 from first dose to study end.

2.3. Exploratory Objectives and Endpoints

Objectives	Endpoints
• 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.

Objectives	Endpoints
• 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). • 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). • 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).

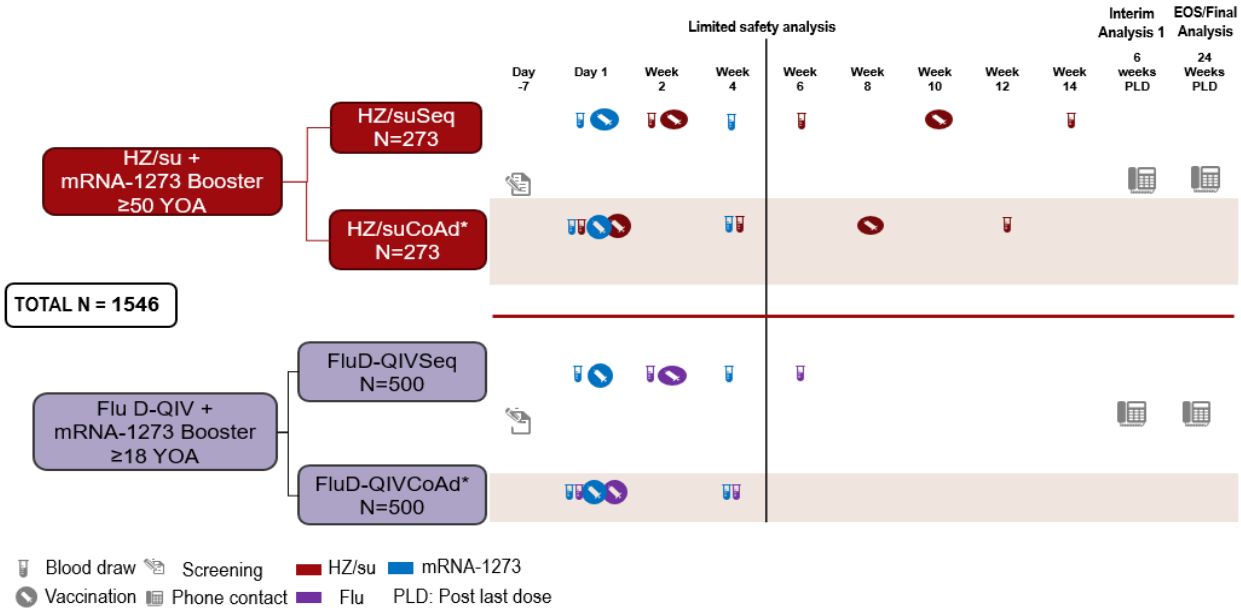
3. Investigational Plan

3.1. Overall Study Design and Plan

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).

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

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 1).

Table 1 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)***

- 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 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.

3.2. Study Endpoints

Please refer to Section 2 of this SAP.

3.3. Treatments

Table 2 Study interventions administered

Study Intervention Name:	**HZ/su**		**Flu D-QIV**	**mRNA-1273**
Product Name:	VZV gE	AS01B	Flu D-QIV 2021-2022 NH	COVID-19 mRNA Vaccine
Study intervention Formulation:	VZV gE (50 µg)	AS01B: 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.

4. General Statistical Considerations

Data will be displayed in all listings sorted by treatment group and cohort.

Continuous data will be described using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). **Categorical data** will be described using the participant count and percentage for each category.

For the **summary statistics** of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean, Confidence Interval (CI) and median will be displayed to one level of precision greater than the data collected. Standard deviation / standard error will be displayed to two levels of precision greater than the data collected.

When count data are presented, percentages/ratio will be rounded to one decimal place. If count is 0 the percentage will be presented as 0.0%. If percentages are 100%, no decimal will be displayed. CI will be presented to two decimal places for proportion/ratio, wherever applicable. A row denoted "Missing" will be included in count tabulations where specified on the shells to account for dropouts and missing values.

The denominator for all percentages will be the number of participants with non-missing values of corresponding parameter in that treatment group or cohort within the analysis population of interest, unless otherwise specified.

Unless otherwise specified, **baseline** will be defined as the last non-missing evaluation prior to first vaccine administration on Day 1, except the HZ/su and Flu D-QIV baseline immunogenicity in participants in the sequential groups which will have Week 2 as baseline.

Study day: If the event is after the first vaccine administration date then the study day will be calculated as assessment date – date of first vaccine administration + 1 else if event is prior to the first vaccine administration date then it will be calculated as assessment date – date of first vaccine.

Calculation regarding antibody concentrations/titers: Antibody values reported as below the lower limit of quantification (LLOQ) will be replaced by 0.5 × LLOQ. Values that are greater than the upper limit of quantification (ULOQ) will be converted to the ULOQ. Missing results will not be imputed.

All statistical analyses will be performed using SAS® software version 9.4 or later.

4.1. Sample Size

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 DQIV-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, see Section 8.1. For the Flu D-QIV and mRNA-1273 booster cohort, success must be achieved for both hypothesis 3 and hypothesis 4; see Section 8.1.

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

4.1.1 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).

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. In such a case, the details of the sample size re-estimation requirements for the HZ/su and mRNA-1273 study cohort will be provided explicitly in a subsequent protocol amendment.

Sample size calculations for the HZ/su and mRNA-1273 booster study cohort can be found in Table 3.

Table 3 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.

A range of non-evaluable rates was explored to demonstrate the power conferred in the event >10% of participants in the study cohort were non-evaluable. See Appendix 14.2.1 for more details.

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

The non-inferiority of Flu D-QIV using GMTs (hypothesis 3, see Section 8.1) 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, see Section 8.2) will be tested using a sequential approach, meaning, hypothesis 3 and 4 (GMT, Flu D-QIV and mRNA-1273 booster primary endpoint), see Section 8.1, must be tested and non-inferiority of Flu D-QIV and mRNA-1273 booster using GMT ratio must be demonstrated before hypothesis 5 (see Section 8.2) 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 (see Section 8.1) is rejected. 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 Flu D-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, the global power 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 4.

Table 4 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.

A range of non-evaluable rates was explored to demonstrate the power conferred in the event >10% of participants in the study cohort were non-evaluable. See Appendix 14.2.2 for more details.

Participants who withdraw from the study will not be replaced.

4.2. Randomization and Stratification

Within each cohort, participants will be centrally randomized in a 1:1 ratio to 1 of the 2 study groups (sequential or co-administration) and receive a Randomization Number through Interactive Response Tool (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. Randomization will be set to ensure at least 69 participants per group will be assigned to the ≥ 70 YOA stratum in the HZ/su and mRNA-1273 booster cohort and at least 75 participants per group will be targeted for assignment to the ≥ 65 YOA stratum in the Flu D-QIV and mRNA-1273 booster cohort.

4.3. Analysis Set

The analysis sets defined in this study are provided in Table 5. 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 Per-Protocol Set (PPS) will be used for analysis of hypothesis 1 and hypothesis 2, see Section 8.1. 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, see Sections 8.1and 8.2.

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 5 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. Note: Subjects qualify for HZ/su PPS and mRNA-1273 PPS independently, meaning, if the criterion to exclude a participant from the HZ/su and mRNA-1273 PPS only applies to one analysis e.g., HZ/su and not mRNA-1273 by virtue of a participant missing the HZ/su primary endpoint blood draw four weeks after the second dose, then the participant will be excluded only from the applicable PPS subset, i.e., in this example, excluded only from the HZ/su PPS subset and maintained in the mRNA-1273 PPS subset..
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. Note: Subjects qualify for Flu D-QIV PPS and mRNA-1273 PPS independently, meaning, if the criterion to exclude a participant from the Flu D-QIV and mRNA-1273 PPS only applies to one analysis e.g., Flu D-QIV and not mRNA-1273 by virtue of a participant missing the Flu D-QIV primary endpoint blood draw four weeks after the Flu D-QIV dose, then the participant will be excluded only from the applicable PPS subset, i.e., in this example, excluded only from the Flu D-QIV PPS subset and maintained in the mRNA-1273 PPS subset.

Participants may be eliminated from the PPS in their respective cohort, if at any point during the study up to the last post dose blood sampling time point, they incur a condition that has the capability of altering their immune response (i.e., an intercurrent medical condition (IMC)) or are confirmed to have an alteration of their initial immune status.

4.4. Subgroups

Subgroup summaries will be presented for many outputs including disposition, demographics, immunogenicity and safety. Subgroups to be used include:

- Age Strata:
  - HZ/su Cohort:
    - 50-59 YOA
    - 60-69 YOA
    - >=70 YOA
  - Flu D-QIV Cohort:
    - 18-64 YOA
    - >=65 YOA
- Gender:
  - All Cohorts:
    - Male
    - Female
- Race:
  - All Cohorts:
    - American Indian or Alaska Native
    - Asian
    - Black or African American
    - White
    - Multiple
    - Other (includes Hawaiian or other Pacific Islander, Other, and Unknown)
- Ethnicity:
  - All Cohorts:
    - Hispanic or Latino
    - Not Hispanic or Latino

Details of which outputs will be presented for each subgroup will be discussed in the respective sections below.

5. Participant Disposition

5.1. Disposition

Participant disposition will be summarized using the Enrolled Set. The summary will include the number and percentage, where possible for the following categories: Enrolled Set, passed screening, screen failures, reasons for screen failure, Randomized Set, reasons for exclusion from Randomized Set to Exposed Set, Exposed Set, exposed to at least one study intervention, exposed to full intervention course, vaccine discontinuation, primary reason for vaccine discontinuation, PPS (HZ/su or Flu D-QIV), mRNA PPS, Excluded from PPS (HZ/su or Flu D-QIV), Excluded from mRNA PPS, reason for exclusion from PPS (HZ/su or Flu D-QIV), reason for exclusion from mRNA PPS, completed study, withdrawal from study, and primary reason for withdrawal from study. The analysis will be presented by cohort, group and overall. In addition, a summary for the Exposed set will be presented excluding the summaries of the Enrolled Set, passed screening, screen failures, reasons for

screen failure, Randomized Set, reasons for exclusion from Randomized Set to Exposed Set, and Exposed Set summaries.

Disposition summaries will be presented for the age strata subgroups defined in Section 4.4.

The number of participants who discontinue vaccine and/or the study by visit (attended/dropout) by reason of discontinuation from study vaccine and reason from withdrawal from study will be presented in a separate table.

Participant disposition data listings will be provided. In addition, the following baseline listings will be provided:

- Informed consent and re-screening
- Inclusion/Exclusion criteria
- Screen Failures

A listing of participants in each analysis set will also be provided.

5.2. Protocol Deviations

Data will be reviewed prior to freezing the database to ensure all deviations leading to analysis set exclusions are captured and categorized in the protocol deviations ADaM dataset. The number of participants with at least one significant protocol deviation as indicated in the PD review log (defined as a protocol deviation that affects primary efficacy and/or safety assessments (as applicable), the safety or mental integrity of a subject, or the scientific value of the trial project), will be summarized by deviation category, cohort, group and overall for Randomized set. The significant protocol deviations will be listed by-participant.

Protocol deviations leading to exclusion from one of the per protocol analysis sets will be summarized by exclusion category in the disposition tables as noted in section 5.1. In addition, the reasons for exclusion will be presented in the analysis set listings.

6. Demographics and Baseline Characteristics

6.1. Demographics

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]).

The demographics and baseline characteristics data collected on the eCRF will be summarized by cohort, group and overall. Listings of participant demographic and baseline characteristics data will be provided to support the summary tables. Summary statistics will be provided descriptively for the following continuous variables:

- Age (year)

A frequency summary (number and percentage) will be provided by treatment group and overall, for the following categorical variables:

- Age strata [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]
- Sex (Male, Female)

  For females,
  - Childbearing potential (Yes/No)
  - Baseline pregnancy test: Urine/Serum (Positive/Negative)
- Race
  - American Indian or Alaska Native
  - Asian:
    - Asian – Central/South Asian Heritage
    - Asian - Japanese Heritage
    - Asian - East Asian Heritage
    - Asian - South East Asian Heritage
  - Black or African American
  - White:
    - White - Arabic/North African Heritage
    - White - White/Caucasian/European Heritage
  - Multiple
  - Other
    - Native Hawaiian or Other Pacific Islander
    - Other
    - Unknown
- Ethnicity
  - Hispanic or Latino
  - Not Hispanic or Latino

Additionally, the summaries above will be presented for the Enrolled Set including the number and percentage of subjects in the additional age category of 18-64; 65-84, ≥85 YOA.

Demographic summaries using the exposed set will be presented for age strata subgroups defined in Section 4.4.

6.2. Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.0, which will be up-versioned to future MedDRA dictionaries as they become available during the study.

Participant medical history data including specific details will be presented in a listing.

7. Treatments and Medications

7.1. Prior and Concomitant Medications (CM)/Vaccinations

All medications/vaccinations will be coded according to the World Health Organization (WHO) drug dictionary WHO Drug Global B3 Mar 2021, which will be updated to future versions whenever they become available during the study. Vaccination history eCRF was designed to collect relevant vaccines received prior before the study. Listing of influenza, COVID-19, and HZ vaccine receipt in addition to other non-study vaccines which will be reported on the CM form will be provided.

Concomitant medication/vaccination is defined as any medication and vaccination (other than study vaccinations) ongoing at the time the first dose of study vaccination is administered or taken on or after the first dose of the study vaccination. Concomitant medications will be listed for each Anatomical Therapeutic Chemical (ATC) class level 4 and preferred term (PT) by cohort and group.

7.2. Study Treatments

The schedule and detail of study intervention administration was displayed in Table 6.

Table 6 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 **Error! Reference source not found.** for the schedule for each of the study groups. Blood sampling to be completed prior to study intervention administration.

Study vaccine compliance will be summarized by cohort and group using the Randomized Set. The analysis will be repeated by age strata for the HZ/su and mRNA-1273 Exposed Set and Flu D-QIV and mRNA-1273 Exposed Set, respectively. In all compliance summaries, the number of participants who received mRNA-1273 booster and all vaccines prescribed for each participant's group will be reported. For the Flu D-QIV and mRNA-1273 booster cohort, compliance with Flu D-QIV vaccination will also be summarized by group. For the HZ/su and mRNA-1273 booster cohort, the summary will present the number and percentage of subjects receiving:

- First vaccination for HZ/su.
- Second vaccination for HZ/su
- Both vaccinations of HZ/su.

Major reasons for non-administration for each vaccine will also be presented with the compliance summaries as well as the reasons for vaccine discontinuation.
A listing of each study vaccine exposure and administration will be provided to present data collected on CRF.

8. Immunogenicity Analysis

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).

All primary, secondary and exploratory immunogenicity endpoint summaries will be repeated using the Exposed Set. In addition, all primary and secondary immunogenicity

endpoint summaries using the applicable PPS and the Exposed Set will be presented for all the subgroups defined in Section 4.4.

8.1. Primary Immunogenicity Endpoint

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.

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

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

The immunogenicity of the HZ/su primary endpoint (Hypothesis 1) will be summarized on the HZ/su PPS.

Anti-gE antibody concentrations will be summarized 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), and expressed as a between-group GMC ratio at 1 month post-dose 2 of HZ/su. The geometric mean with 95% CI, geometric standard deviation along with median, minimum, maximum derived from the original data will be presented in the table. The geometric mean and geometric standard deviation calculations will be performed by taking the anti-log of the mean and standard deviation of the log10 transformed concentration data.

For anti-gE at 1 month post-dose 2 of HZ/su, the least square point estimate and its 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 to demonstrate non-inferiority of the HZ/suCoAd vs. HZ/suSeq for the HZ/su immune response. 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.

Anti-gE antibody concentrations at all time points (pre-vaccination, 1 month post-dose 1 and 1 month post-dose 2) will be displayed using reverse cumulative curves.

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

The immunogenicity assessment of the mRNA-1273 booster primary endpoint (Hypothesis 2) will be summarized on the mRNA-1273 PPS.

Anti-S Protein antibody concentrations will be summarized at pre-vaccination (Day 1) and at 1 month post mRNA-1273 booster dose (at Week 4 for both groups, HZ/suSeq and HZ/suCoAd), and expressed as a between-group GMC ratio at 1 month post mRNA-1273 booster dose. The geometric mean and geometric standard deviation by anti-log10 transformation, along with median, minimum, maximum derived from the original data will be presented in the table.

For anti-S Protein at 1 month post mRNA-1273 booster dose, the least square point estimate and its 95% CI of the between group GMC ratios will be computed using ANCOVA model on the log10 transformation of the concentrations to demonstrate non-inferiority of the HZ/suCoAd vs. HZ/suSeq for the HZ/su immune response. 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.

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

Flu D-QIV immunogenicity (anti-HI antibodies)

The immunogenicity assessment of the Flu D-QIV primary endpoint (Hypothesis 3) will be summarized on the Flu D-QIV PPS.

Anti-HI antibody titers against each of 4 influenza strains included in Flu D-QIV will be summarized at pre-vaccination vaccination (at Day 1 for FluD-QIVCoAd, at Week 2 for FluD-QIVSeq) and at 1 month post Flu D-QIV (at Week 6 for FluD-QIVSeq, at Week 4 for FluD-QIVCoAd), and expressed as a between-group GMT ratio at 1 month post Flu D-QIV. The geometric mean and geometric standard deviation by anti-log10 transformation, along with median, minimum, maximum derived from the original data will be presented in the table.

To demonstrate non-inferiority of the FluD-QIVCoAd vs. FluD-QIVSeq for the Flu D-QIV immune response in terms of anti-HI antibody GMTs, the least square point estimate and its 95% CI of the between-group GMT ratios post-dose 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.

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

The immunogenicity assessment of the mRNA-1273 primary endpoint (Hypothesis 4) will be summarized for the mRNA-1273 PPS.

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

booster dose. The geometric mean and geometric standard deviation by anti-log10 transformation, along with median, minimum, maximum derived from the original data will be presented in the table.

For anti-S Protein at 1 month post mRNA-1273 booster dose, the least square point estimate and its 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 to demonstrate non-inferiority of the FluD-QIVCoAd vs. FluD-QIVSeq for the Flu D-QIV immune response. 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.

8.2. Secondary Immunogenicity Endpoint

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.

8.2.1. Secondary Endpoints for Flu D-QIV immunogenicity (Anti-HI antibody SCRs)

The immunogenicity assessment of the Flu D-QIV secondary endpoint (Hypothesis 5) will be summarized for the Flu D-QIV PPS.

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

To demonstrate non-inferiority of the FluD-QIVCoAd vs. FluD-QIVSeq for the Flu D-QIV immune response 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 DQIV (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).Descriptive immune endpoints

8.2.2.1 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 strata (50-59, 60-69, ≥ 70 YOA) at baseline and at 1 month post-dose 2 of HZ/su (at Week 14 for HZ/suSeq, at Week 12 for HZ/suCoAd) for the HZ/su PPS.

- VRR with exact 95% CI at 1 month post-dose 2 of HZ/su
  - The VRR for anti-gE post-dose 2 is defined as the percentage of participants who have at least:
    - 4-fold increase in the post-dose anti-gE antibody concentration as compared to the pre-vaccination anti-gE antibody concentration, for participants who are seropositive at pre-vaccination, or,
    - A 4-fold increase in the post-dose anti-gE antibody concentration as compared to the anti-gE antibody cut-off value of 97 mIU/mL 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 anti-gE antibody concentration is greater than or equal to the assay cutoff 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 at all time points (pre, Dose 1 and Dose 2) will be displayed using reverse cumulative curves.

- MGI in anti-gE antibody 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 enzyme linked immunosorbent assay (ELISA) concentrations.

- The distribution of the fold increase in anti-gE antibody ELISA concentrations 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.

8.2.2.2 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 strata (50-59, 60- 69, ≥ 70 YOA for HZ/su and mRNA-1273 booster cohort; 18-64 and ≥ 65 YOA for Flu DQIV and mRNA-1273 booster cohort). All summaries will be provided for the mRNA-1273 PPS by cohort.

- 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).

8.2.2.3 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 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). 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).

- 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 pre-vaccination 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.

8.3. Exploratory Immunogenicity Endpoints

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 8.2.2.1. The summary of this data will use HZ/su PPS. This summary will not be in the initial study report as it will only be conducted once the results of study report are reviewed and if needed, additional lab results obtained.

Neutralizing antibodies for SARS-CoV-2 (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. Summaries will be produced for the mRNA-1273 PPS per cohort.

Descriptive humoral immune responses to vaccination and/or SARS-CoV-2 infection for anti-RBD protein:

- 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]). Summaries will be produced for the mRNA-1273 PPS per cohort.

Descriptive humoral immune responses to SARS-CoV-2 infection for anti-N:

- 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 postvaccination OR for a participant seropositive at baseline, a 4-fold or more increase post-vaccination. Summaries will be produced for the mRNA-1273 PPSper cohort.

9. Safety Analysis

Safety analysis includes solicited AEs, unsolicited AEs, SAEs, pIMDs, AESIs, COVID-19 cases, HZ episodes/cases, pregnancy tests and pregnancy events/outcomes. The safety endpoints will be summarized for each cohort on the HZ/su and mRNA-1273 Exposed Set and on the Flu D-QIV and mRNA-1273 Exposed Set, respectively. PIMDs, and HZ episodes/cases will be summarized on the HZ/su and mRNA-1273 Exposed Set only. All the safety analyses under the secondary objective are descriptive. Subgroup analyses by age strata (as applicable to each study cohort), gender, race, and ethnicity as defined in Section 4.4 will be performed on select AE summaries.

9.1. Adverse Events

The timeframes for collecting and reporting the safety information are provided in Table 7.

Table 7 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
Unsolicited AEs	Day 1 through Day 30 following each study intervention administration
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

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

9.1.1. Solicited Adverse Events

Solicited AEs are pre-specified local and systemic adverse events. Solicited AEs will be collected through 7 days following each vaccination. Solicited AEs with onset during the 7-day solicitation period that continue beyond the 7-day period will be reported as solicited AEs. The solicited AEs will be collected using the diary eCRFs.

Participant's compliance with respect to the diary card based on the Exposed Set will be determined separately for local and systemic events for the following:

- Number of participants who did not present diary data at all
- Number of participants who completed diary card, regardless of visit
- Number of participants who completed diary card for each day of the first 7 days post any vaccination (i.e., Day 1, Day 2, Day 3, Day 4, Day 5, Day 6 and Day 7)

A sensitivity analysis to exclude participants who may not have acceptable diary data or certain missing diary records may be performed.

Per the study design and diary forms, participants who receive the administration of the mRNA-1273 booster vaccine on Day 1, have until Day 14 (Week 2) to receive the next vaccine administration. As such, all solicited systemic AEs that occurred on or after mRNA-1273 booster vaccine but prior to HZ/su or Flu D-QIV vaccine administration on Day 14 (Week 2) are deemed to be attributable to the mRNA-1273 booster vaccine. For participants in the sequential groups (HZ/suSeq, FluD-QIVSeq), the diary forms are re-set at the time of first HZ/su or Flu D-QIV vaccination on Day 14 (Week 2) to collect solicited systemic AEs that are either ongoing from mRNA-1273 booster vaccine from Day 1 or occurred on or after the first HZ/su or Flu D-QIV vaccination on Day 14 (Week 2). The diary data is therefore setup to ensure that any solicited systemic AE attributable to each of the following vaccines only: mRNA-1273 booster, first HZ/su, second HZ/su or Flu D-QIV, can be determined depending on the time of the AE relative to the time of each vaccine administration, and prior to the date of any subsequent vaccination. Solicited local AEs are collected in separate diaries per vaccine received and will be attributed to the appropriate based on the diary used.

For data analysis purposes, the CoAd groups (HZ/suCoAd, FluD-QIVCoAd) will be presented as a single column, with the exception of the HZ/suCoAd group that certain selected outputs will be displayed by the first and second HZ/su vaccine doses respectively.

For the sequential groups (HZ/suSeq, FluD-QIVSeq), data will be presented by the individual vaccines as follows:

- A column for mRNA-1273 booster vaccine on Day 1,
- A column for either HZ/su or FluD-QIV vaccine on Day 14 (Week 2) depending on the sequential group,

- A column labelled "Overlapping" to count participants with events that occurred on or after post mRNA booster vaccine dose given at Day 1 and are ongoing after receiving the first HZ/su or Flu D-QIV at Day 14 (Week 2)
- A column labelled either "mRNA-1273 or HZ/su" or "mRNA-1273 or Flu D-QIV" depending on the sequential group, that counts the number of events that each participant experienced under mRNA-1273 or HZ/su vaccine for HZ/SuSeq group or under mRNA-1273 or Flud-QIV vaccine for FluD-QIVSeq group. For participants with overlapping AEs, their events are counted once at maximum severity for any vaccination.

In addition, and specifically for the HZ/su groups (HZ/suSeq, HZ/suCoAd), selected outputs will be displayed by the first and second HZ/su vaccine doses administered within each HZ/suSeq and HZ/suCoAd treatment groups respectively.

The duration of each solicited adverse event will be calculated following the process below:

- the diary data is setup in Study Data Tabulation Model (SDTM) to capture separately events that occurred within the first 7 days and events that occurred longer than 7 days. The 2 datasets are set together.
- Then for each solicited AE that occurred following each vaccination, duration is calculated as sum of the unique number of days of the solicited AE with greater than zero grade

The following specific solicited adverse events will be assessed.
Local solicited AEs:

- Pain
- Redness
- Swelling
- Pruritus
- Axillary (underarm) swelling or tenderness ipsilateral to the injection site

Systemic solicited AEs:

- Fatigue
- Myalgia
- Headache
- Shivering/chills
- Fever
- Gastrointestinal (GI) symptoms (nausea, vomiting, diarrhea and/or abdominal pain). Each symptom under GI will be presented separately and then collectively as GI. For intensity for GI, the highest intensity among all these 4 symptoms will be used. For example – if a subject experiences grade 1 nausea, grade 2 vomiting, grade 3 diarrhea and grade 2 abdominal pain, then the intensity for GI for the subject will be presented as the highest, i.e., grade 3.

- Arthralgia

The solicited AEs will be MedDRA coded to the following SOCs/PTs for a summary by SOCs and PTs combining solicited and unsolicited AEs for all study groups (HZ/suSeq, HZ/suCoAd, FluD-QIVSeq, FluD-QIVCoAd).

Solicited AE	System Organ Class Code	System Organ Class	Preferred Term Code	Preferred Term
Abdominal Pain	10017947	Gastrointestinal disorders	10000081	Abdominal pain
Arthralgia	10028395	Musculoskeletal and connective tissue disorders	10003239	Arthralgia
Chills	10018065	General disorders and administration site conditions	10008531	Chills
Diarrhoea	10017947	Gastrointestinal disorders	10012735	Diarrhoea
Fatigue	10018065	General disorders and administration site conditions	10016256	Fatigue
Headache	10029205	Nervous system disorders	10019211	Headache
Injection Site Erythema	10018065	General disorders and administration site conditions	10022061	Injection site erythema
Injection Site Induration/ Swelling	10018065	General disorders and administration site conditions	10053425	Injection site swelling
Injection Site Pain	10018065	General disorders and administration site conditions	10022086	Injection site pain
Myalgia	10028395	Musculoskeletal and connective tissue disorders	10028411	Myalgia
Nausea	10017947	Gastrointestinal disorders	10028813	Nausea
Pruritus	10040785	Skin and subcutaneous tissue disorders	10022093	Injection site pruritus
Underarm Gland Swelling or Tenderness	10005329	Blood and lymphatic system disorders	10025197	Lymphadenopathy

Vomiting	10017947	Gastrointestinal disorders	10047700	Vomiting
Fever	10018065	General disorders and administration site conditions	10037660	Pyrexia

The number and percentage of participants with at least 1 solicited local event, with at least 1 solicited systemic event and any solicited event as well as each solicited local and solicited systemic AE (within onset within Days 1-7) will be tabulated with exact 95% CIs, for each vaccination visit and overall for all study groups (HZ/suSeq, HZ/suCoAd, FluD-QIVSeq, FluD-QIVCoAd). Similar summaries will be provided for participants with Grade 3 events, medically attended solicited local events, and medically attended solicited systemic events. These summaries will be presented for all the subgroups defined in Section 4.4.

The duration in days of the solicited AEs, both local (for each vaccine separately) and systemic, with onset within 7-days following each vaccination visit and overall (total duration) will be calculated and summarized by mean, median, standard deviation, and range. Similar summaries will be provided for participants with Grade 3 events. These summaries will be presented for age strata subgroups defined in Section 4.4.

In addition, the following below will be presented:

- The percentage of subjects with solicited local adverse events lasting longer than 7 days and duration in days (total) of solicited local adverse events lasting longer than 7 days following each vaccination visit

- The percentage of subjects with solicited systemic adverse events lasting longer than 7 days and duration in days (total) of systemic adverse events lasting longer than 7 days following each vaccination visit

- Both of the above summaries will be presented for age strata subgroups defined in Section 4.4.

- The number of each systemic adverse event (any, grade 3 and medically attended) following Dose 1 of HZ/su or Flu D-QIV and mRNA-1273 vaccination for all groups. For example, if a participant has 2 or more recorded events of the same type then each event is counted.

Separate individual data listings for solicited local adverse events and solicited systemic events will be provided.

9.1.2. Unsolicited Adverse Events

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.

The number and percentage of participants reporting unsolicited AEs classified by MedDRA primary SOC and 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.

Summaries of unsolicited AEs within the 14-day window following Dose 1 and 30-day window following each dose and overall will also be presented for all subgroups defined in Section 4.4.

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

Summaries of medically-attended unsolicited AEs and related medically-attended unsolicited AEs within the 14-day and 30-day windows following Dose 1 of HZ/su and mRNA-1273 vaccination and following Flu D-QIV and mRNA-1273 vaccination will be presented for all subgroups defined in Section 4.4. The other AE summaries will be presented for age strata subgroups defined in Section 4.4.

9.1.3. Serious Adverse Events

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

Summaries of SAEs up to 30 days post-last vaccination and from first vaccination up to study end will also be presented for all subgroups defined in Section 4.4. The other SAE summaries will also be presented for age strata subgroups defined in Section 4.4.

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

pIMDs include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune etiology. See Table 23 of study protocol dated 21September 2021, for a list of potential pIMDs.

The number and percentage of participants reporting pIMDs on the CRF from first vaccination up to 30 days post-last vaccination and from first vaccination up to study end will be summarized for both study groups in the HZ/su and mRNA-1273 booster cohort (HZ/suSeq, HZ/suCoAd, overall). All pIMDs will be summarized by MedDRA SOC and PT. Any related pIMDs will also be summarized for study groups (HZ/suSeq, HZ/suCoAd and overall).

Summaries of pIMDs from first vaccination up to study end will also be presented for all subgroups defined in Section 4.4. Summaries of pIMDs and related pIMDs up to 30 days post-last vaccination and related pIMDs from first vaccination up to study end will also be presented for age strata subgroups defined in Section 4.4.

All pIMDs will be listed.

9.1.5. Adverse events of special interest (AESI)

The number and percentage of participants reporting AESIs on the CRF 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.

Summaries of AESIs from first vaccination up to study end will also be presented for all subgroups defined in Section 4.4. Summaries of AESIs and related AESIs up to 30 days post-last vaccination and related AESIs from first vaccination up to study end will also be presented for age strata subgroups defined in Section 4.4.

A listing of AESIs will also be presented.

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

The number and percentage of participants reporting the following:

- Suspected HZ episodes,
- With at least one lesion sample collected for suspected HZ episode, and
- Confirmed HZ episode

from first dose to study end will be summarized for the HZ/suSeq and HZ/suCoAd study groups. All potential HZ episodes and lesion sampling throughout the entire study period will be listed.

9.1.7. Confirmed HZ episodes (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). The analysis of this data will be restricted to the cases where lesion sample is taken and will follow the suspected HZ episodes discussed in Section 9.1.6.

9.1.8. 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.

Diagnosis and categorization of COVID-19 cases for reporting purposes would 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.

COVID-19 cases by primary case definition, secondary case definition, and tertiary case definition identified on the CRF AE pages will be summarized by number and percentage of participants from first dose to study end for all study groups (HZ/suSeq, HZ/suCoAd, FluD-QIVSeq, FluD-QIVCoAd and overall) and COVID-19 cases will also be listed.

9.1.9. 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 from the notification eCRFs.

9.1.10. 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).

Medical device AE will be recorded on the AE forms as adverse device effect (ADE), serious adverse device effect (SADE) and unanticipated SADE (USADE) and summarized by the number and percent of participants that experience a given event.

10. Safety analysis for Safety Review Team review

The safety review team (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. PPD preclarus dashboard will also be used to generate the required outputs for SRT review to help decide on continuation of enrollment in the co-administration groups. Periodic analyses will be done for regular SRT review. All SRT analyses will be descriptive.

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. The outputs selected for limited safety analyses will be programmed as TFL outputs using SAS® software version 9.4 or later.

11. Interim Analysis

One formal interim analysis (IA) of safety and reactogenicity data was conducted. The safety objectives were assessed independently for the two cohorts (HZ/su and mRNA-1273 booster, Flu D-QIV and mRNA-1273 booster) at the IA when the last active participant enrolled in both cohorts complete their 6 weeks post-last dose of study vaccine Phone Contact 1.

Analyses were performed on data as clean as possible and an interim report was provided. The IA included:

- Solicited AE 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 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.

No hypothesis testing was conducted as part of the safety IA.

The final analysis will include safety follow-up up to 6 months post the last vaccine dose.

No IA was conducted for the immunogenicity data for either cohort as this data was not available at the timepoints set for the safety and reactogenicity data IA.

12. Changes in the Planned Analysis

Since the immunogenicity results were not available in time, the interim analysis was restricted to safety and reactogenicity data and did not include immunogenicity data as was originally planned per protocol.

The solicited systemic eDiary was unable to be programmed to shut off post-day 7 following vaccination assuming there were no ongoing events reported, which meant that these events were solicited daily for 30 days post-vaccination, even if they were not ongoing after 7 days post-vaccination. Since, as per protocol, any adverse event with an onset more than 7 days and up to 30 days post-vaccination was to be reported as an 'unsolicited AE', the AEs meeting this definition entered in the eDiaries were transcribed by the site staff to the unsolicited AE eCRF page and will be subsequently analyzed as such and not counted as solicited AEs in the safety analyses.

In Table 4 of the protocol, interval ranges between certain visits were provided whereby if the visits were to happen beyond these specified intervals, participants may not have been eligible for inclusion in the applicable Per Protocol Set (PPS). The out of window intervals in Table 8 and Table 9 below represent the actual limits that will be used in the final analyses.

Table 8 Intervals between study visits for HZ/su and mRNA-1273 booster cohort

Interval	Planned Visit Interval	Allowed Interval Range to Remain in PPS
HZ/suSeq group		
Pre-vaccination → Visit 1	-7 days	No impact on PPS
Visit 1→Visit 2	14 days	13-49
Visit 1→Visit 3	28 days	25-49
Visit 2→Visit 4	28 days	No impact on PPS
Visit 2→Visit 5	56 days	48-83
Visit 5→Visit 6	28 days	25-49
Visit 5→Phone contact 1	42 days	No impact on PPS

Interval	Planned Visit Interval	Allowed Interval Range to Remain in PPS
Visit 5→Phone contact 2	168 days	No impact on PPS
HZ/suCoAd group		
Pre-vaccination → Visit 1	-7 days	No impact on PPS
Visit 1→Visit 2	28 days	25-49
Visit 1→Visit 3	56 days	48-83
Visit 3→Visit 4	28 days	25-49
Visit 3→Phone contact 1	42 days	No impact on PPS

Table 9 Intervals between study visits for Flu D-QIV and mRNA-1273 booster cohort

Interval	Planned Visit Interval	Allowed Interval Range to Remain in PPS
FluD-QIVSeq group		
Pre-vaccination → Visit 1	-7 days	No impact on PPS
Visit 1→Visit 2	14 days	13-42 days
Visit 1→Visit 3	28 days	21-42 days
Visit 2→Visit 4	28 days	21-42 days
Visit 2→Phone contact 1	42 days	No impact on PPS
Visit 2→Phone contact 2	168 days	No impact on PPS
FluD-QIVCoAd group		
Pre-vaccination → Visit 1	-7 days	No impact on PPS
Visit 1→Visit 2	28 days	21-42 days
Visit 1→Phone contact 1	42 days	No impact on PPS
Visit 1→Phone contact 2	168 days	No impact on PPS

13. References

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14. Appendices

14.1. Schedule of Activities

See Table 1 of study protocol.

14.2. Additional Power Details

14.2.1. HZ Cohort

The primary power and sample size calculation assumes 10% of the participants randomized are non-evaluable (e.g. due to drop out/protocol violation). A range of non-evaluable rates were explored to demonstrate the power conferred by fewer evaluable participants in the study. The global power to meet both non-inferiority primary endpoints in the HZ/su and mRNA-1273 booster cohort is maintained approximately 80% or above for non-evaluable rates of 30% or less.

Primary Endpoint Non-inferiority*	Non-evaluable Rate	Number of Evaluable Participants per Group	α (1-sided test)	Standard Deviation	Reference δ Assumed	NI δ	Total β	Power	Global β to show non-inferiority of the primary endpoints	Global power for the primary endpoints
Post-Dose 2 HZ/su GMC Ratio (Sequential vs. Co-Ad) anti-gE	15%	232	0.025	0.35	1.1	1.5	1.5%	98.5%	~12%	~88%
mRNA booster GMC Ratio (Sequential vs. Co-Ad) anti-S	15%	232	0.025	0.45	1.1	1.5	10.4%	89.6%		
Post-Dose 2 HZ/su GMC Ratio (Sequential vs. Co-Ad) anti-gE	18%	224	0.025	0.35	1.1	1.5	1.8%	98.2%	~13%	~87%
mRNA booster GMC Ratio (Sequential vs. Co-Ad) anti-S	18%	224	0.025	0.45	1.1	1.5	11.5%	88.5%		
Post-Dose 2 HZ/su GMC Ratio (Sequential vs. Co-Ad) anti-gE	20%	218	0.025	0.35	1.1	1.5	2.1%	97.9%	~15%	~85%
mRNA booster GMC Ratio (Sequential vs. Co-Ad) anti-S	20%	218	0.025	0.45	1.1	1.5	12.3%	87.7%		
Post-Dose 2 HZ/su GMC Ratio (Sequential vs. Co-Ad) anti-gE	25%	205	0.025	0.35	1.1	1.5	2.7%	97.3%	~17%	~83%
mRNA booster GMC Ratio (Sequential vs. Co-Ad) anti-S	25%	205	0.025	0.45	1.1	1.5	14.4%	85.6%		

Post-Dose 2 HZ/su GMC Ratio (Sequential vs. Co-Ad) anti-gE	30%	191	0.025	0.35	1.1	1.5	3.7%	96.3%	~20%	80%
mRNA booster GMC Ratio (Sequential vs. Co-Ad) anti-S	30%	191	0.025	0.45	1.1	1.5	16.9%	83.1		

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)).

14.2.2. Flu Cohort

The primary power and sample size calculation assumes 10% of the participants randomized are non-evaluable (e.g. due to drop out/protocol violation). A range of non-evaluable rates were explored to demonstrate the power conferred by fewer evaluable participants in the study. The global power to meet both non-inferiority primary endpoints in the Flu D-QIV and mRNA-1273 booster cohort is maintained approximately 80% or above for non-evaluable rates of 25% or less.

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 75% across all of the non-evaluable rates explored (10%-30%).

Primary Endpoint Non-inferiority*	Non-evaluable Rate	Number of Evaluable Participants per Group	α (1-sided test)	Standard Deviation	Reference δ Assumed	NI δ	Total β	Power	Global β to show non-inferiority of the primary endpoints	Global power for the primary endpoints
FLU D-QIV GMT Ratio (Sequential vs. Co-Ad) – A/ H1N1 strain	10%	450	0.025	0.6	1.04	1.5	2.2%	97.8%	~9.1%	~90.1%
FLU D-QIV GMT Ratio (Sequential vs. Co-Ad) – A/H3N2 strain	10%	450	0.025	0.6	1.04	1.5	2.2%	97.8%		
FLU D-QIV GMT Ratio (Sequential vs. Co-Ad) – B/Victoria lineage	10%	450	0.025	0.6	1.04	1.5	2.2%	97.8%		
FLU D-QIV GMT Ratio (Sequential vs. Co-Ad) – B/Yamagata lineage	10%	450	0.025	0.6	1.04	1.5	2.2%	97.8%		
mRNA-1273 booster GMC Ratio (Sequential vs. Co-Ad)	10%	450	0.025	0.45	1.1	1.5	0.6%	99.4%		
FLU D-QIV GMT Ratio (Sequential vs. Co-Ad) – A/ H1N1 strain	15%	425	0.025	0.6	1.04	1.5	2.8%	97.2%	~11.5%	~88.5%
FLU D-QIV GMT Ratio (Sequential vs. Co-Ad) – A/H3N2 strain	15%	425	0.025	0.6	1.04	1.5	2.8%	97.2%		
FLU D-QIV GMT Ratio (Sequential vs. Co-Ad) – B/Victoria lineage	15%	425	0.025	0.6	1.04	1.5	2.8%	97.2%		
FLU D-QIV GMT Ratio (Sequential vs. Co-Ad) – B/Yamagata lineage	15%	425	0.025	0.6	1.04	1.5	2.8%	97.2%		
mRNA-1273 booster GMC Ratio (Sequential vs. Co-Ad)	15%	425	0.025	0.45	1.1	1.5	0.8%	99.2%		
FLU D-QIV GMT Ratio (Sequential vs. Co-Ad) – A/ H1N1 strain	18%	410	0.025	0.6	1.04	1.5	3.3%	96.7%	~13.4%	~86.6%

FLU D-QIV GMT Ratio (Sequential vs. Co-Ad) – A/H3N2 strain	18%	410	0.025	0.6	1.04	1.5	3.3%	96.7%		
FLU D-QIV GMT Ratio (Sequential vs. Co-Ad) – B/Victoria lineage	18%	410	0.025	0.6	1.04	1.5	3.3%	96.7%		
FLU D-QIV GMT Ratio (Sequential vs. Co-Ad) – B/Yamagata lineage	18%	410	0.025	0.6	1.04	1.5	3.3%	96.7%		
mRNA-1273 booster GMC Ratio (Sequential vs. Co-Ad)	18%	410	0.025	0.45	1.1	1.5	1.0%	99.0%		
FLU D-QIV GMT Ratio (Sequential vs. Co-Ad) – A/ H1N1 strain	20%	400	0.025	0.6	1.04	1.5	3.7%	96.3%		
FLU D-QIV GMT Ratio (Sequential vs. Co-Ad) – A/H3N2 strain	20%	400	0.025	0.6	1.04	1.5	3.7%	96.3%		
FLU D-QIV GMT Ratio (Sequential vs. Co-Ad) – B/Victoria lineage	20%	400	0.025	0.6	1.04	1.5	3.7%	96.3%	~15%	~85%
FLU D-QIV GMT Ratio (Sequential vs. Co-Ad) – B/Yamagata lineage	20%	400	0.025	0.6	1.04	1.5	3.7%	96.3%		
mRNA-1273 booster GMC Ratio (Sequential vs. Co-Ad)	20%	400	0.025	0.45	1.1	1.5	1.2%	98.8%		
FLU D-QIV GMT Ratio (Sequential vs. Co-Ad) – A/ H1N1 strain	25%	375	0.025	0.6	1.04	1.5	4.8%	95.2%		
FLU D-QIV GMT Ratio (Sequential vs. Co-Ad) – A/H3N2 strain	25%	375	0.025	0.6	1.04	1.5	4.8%	95.2%	~19.2%%	~80.8%
FLU D-QIV GMT Ratio (Sequential vs. Co-Ad) – B/Victoria lineage	25%	375	0.025	0.6	1.04	1.5	4.8%	95.2%		
FLU D-QIV	25%	375	0.025	0.6	1.04	1.5	4.8%	95.2%		

GMT Ratio (Sequential vs. Co-Ad) – B/Yamagata lineage										
mRNA-1273 booster GMC Ratio (Sequential vs. Co-Ad)	25%	375	0.025	0.45	1.1	1.5	1.6%	98.4%		
FLU D-QIV GMT Ratio (Sequential vs. Co-Ad) – A/ H1N1 strain	30%	350	0.025	0.6	1.04	1.5	6.1%	93.9%	~24%	~76%
FLU D-QIV GMT Ratio (Sequential vs. Co-Ad) – A/H3N2 strain	30%	350	0.025	0.6	1.04	1.5	6.1%	93.9%		
FLU D-QIV GMT Ratio (Sequential vs. Co-Ad) – B/Victoria lineage	30%	350	0.025	0.6	1.04	1.5	6.1%	93.9%		
FLU D-QIV GMT Ratio (Sequential vs. Co-Ad) – B/Yamagata lineage	30%	350	0.025	0.6	1.04	1.5	6.1%	93.9%		
mRNA-1273 booster GMC Ratio (Sequential vs. Co-Ad)	30%	350	0.025	0.45	1.1	1.5	2.3%	97.7%		
FLU D-QIV Non-inferiority* – 4 Strains – Secondary Endpoint on SCR difference										
Secondary Endpoint	**Non-Evaluable Rate**	**Number of Evaluable Participants per Group**	**α (1-sided test)**	**Threshold**	**SCR Assumed**	**Total b**	**Power**			
SCR difference (Sequential vs. Co-Ad) – A/H1NI strain	10%	450	0.025	10%	78.6%	4.5%	95.5%			
SCR difference (Sequential vs. Co-Ad) – A H3N2 strain	10%	450	0.025	10%	70.3%	9.2%	90.8%			
SCR difference (Sequential vs. Co-Ad) – B/Victoria lineage	10%	450	0.025	10%	53.8%	14.9%	85.1%			
SCR difference (Sequential vs. Co-Ad) B/Yamagata lineage	10%	450	0.025	10%	56.9%	14.0%	86.0%			

SCR difference (Sequential vs. Co-Ad) – A/H1NI strain	15%	425	0.025	10%	78.6%	5.6%	94.4%		
SCR difference (Sequential vs. Co-Ad) – A H3N2 strain	15%	425	0.025	10%	70.3%	10.8%	89.2%		
SCR difference (Sequential vs. Co-Ad) – B/Victoria lineage	15%	425	0.025	10%	53.8%	15.9%	84.1%		
SCR difference (Sequential vs. Co-Ad) B/Yamagata lineage	15%	425	0.025	10%	56.9%	15.8%	84.2%		
SCR difference (Sequential vs. Co-Ad) – A/H1NI strain	18%	410	0.025	10%	78.6%	6.3%	93.7%		
SCR difference (Sequential vs. Co-Ad) – A H3N2 strain	18%	410	0.025	10%	70.3%	11.9%	88.1%		
SCR difference (Sequential vs. Co-Ad) – B/Victoria lineage	18%	410	0.025	10%	53.8%	17.2%	82.8%		
SCR difference (Sequential vs. Co-Ad) B/Yamagata lineage	18%	410	0.025	10%	56.9%	17.1%	82.9%		
SCR difference (Sequential vs. Co-Ad) – A/H1NI strain	20%	400	0.025	10%	78.6%	6.9%	93.1%		
SCR difference (Sequential vs. Co-Ad) – A H3N2 strain	20%	400	0.025	10%	70.3%	12.8%	87.2%		
SCR difference (Sequential vs. Co-Ad) – B/Victoria lineage	20%	400	0.025	10%	53.8%	19.8%	81.2%		
SCR difference (Sequential vs. Co-Ad) B/Yamagata lineage	20%	400	0.025	10%	56.9%	19.6%	81.4%		

SCR difference (Sequential vs. Co-Ad) – A/H1NI strain	25%	375	0.025	10%	78.6%	8.5%	91.5%		
SCR difference (Sequential vs. Co-Ad) – A H3N2 strain	25%	375	0.025	10%	70.3%	14.9%	85.1%		
SCR difference (Sequential vs. Co-Ad) – B/Victoria lineage	25%	375	0.025	10%	53.8%	12.0%	78.0%		
SCR difference (Sequential vs. Co-Ad) B/Yamagata lineage	25%	375	0.025	10%	56.9%	10.7%	79.3%		
SCR difference (Sequential vs. Co-Ad) – A/H1NI strain	30%	350	0.025	10%	78.6%	10.4%	89.6%		
SCR difference (Sequential vs. Co-Ad) – A H3N2 strain	30%	350	0.025	10%	70.3%	11.3%	82.7%		
SCR difference (Sequential vs. Co-Ad) – B/Victoria lineage	30%	350	0.025	10%	53.8%	23.6%	76.4%		
SCR difference (Sequential vs. Co-Ad) B/Yamagata lineage	30%	350	0.025	10%	56.9%	23.4%	76.6%		

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.

GlaxoSmithKline Biologicals SA (GSK)

217670 (ZOSTER-091)

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

03DEC2021

Draft Statistical Analysis Plan

Version *1.0*

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TABLE OF CONTENTS

List of Abbreviations

AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CBER	Center for Biologics Evaluation and Research
CI	Confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
DBF	database freeze
ECG	electrocardiogram
FAS	full analysis set
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 DQIV dose
gE	glycoprotein E
GI	gastrointestinal
GMC	geometric mean concentration
GMT	geometric mean titer
HI	hemagglutinin inhibition
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
IA	interim analysis
IMC	intercurrent medical condition
IRT	interactive response tool
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MGI	mean geometric increase
MPL	3-O-desacyl-4'-monophosphoryl lipid A
mRNA	messenger ribonucleic acid
mRNA-1273	mRNA-based vaccine against COVID-19
PCR	Polymerase chain reaction
pIMD	potential immune mediated disease
PPS	per protocol set
PT	preferred term
RBD	Receptor binding domain
SAE	serious adverse event

SAP	statistical analysis plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SOC	system organ class
SCR	seroconversion rate
S-protein	spike protein
SPR	seroprotection rate
SRT	safety review team
su	subunit
ULOQ	Upper limit of quantification
VRR	vaccine response rate
VZV	varicella zoster virus
WHO	World Health Organization
YOA	years of age

1. Introduction

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).

This statistical analysis plan (SAP) is developed to provide the details of the planned statistical methodology for both the interim analysis and final analysis (used for the preparation of final study report after database lock). It is based upon the final protocol amendment version date 21 September 2021. The SAP is finalized prior to data analysis start. Major changes in the analysis that are made after database lock will be documented in the Clinical Study Report along with the rationale and other details.

2. Objectives

2.1. Primary Objective and Endpoints

Objectives	Endpoints
• 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).

§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.

2.2. Secondary Objectives and Endpoints

Objectives	Endpoints
Secondary – Immunogenicity	
• 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% confidence interval (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).

Objectives	Endpoints
Secondary – Immunogenicity	
• 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 seroprotection rate (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). • 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 years of age [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
Secondary – Safety/Reactogenicity	
• 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**: o 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. o 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)**: o Number and percentage of participants reporting SAEs from first dose up to 30 days post-last dose within each group. o 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:** o Number and percentage of participants reporting of pIMDs from first dose up to 30 days post-last dose within each group. o Number and percentage of participants reporting pIMDs from first dose to study end. • **Adverse events of special interest (AESIs):** o Number and percentage of participants reporting AESIs from first dose up to 30 days post-last dose within each group. o 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**: Number and percentage of participants meeting case definitions of COVID-19 from first dose to study end.

[a]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.

2.3. Exploratory Objectives and Endpoints

Objectives	Endpoints
• 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.

Objectives	Endpoints
• 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). • 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). • 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).

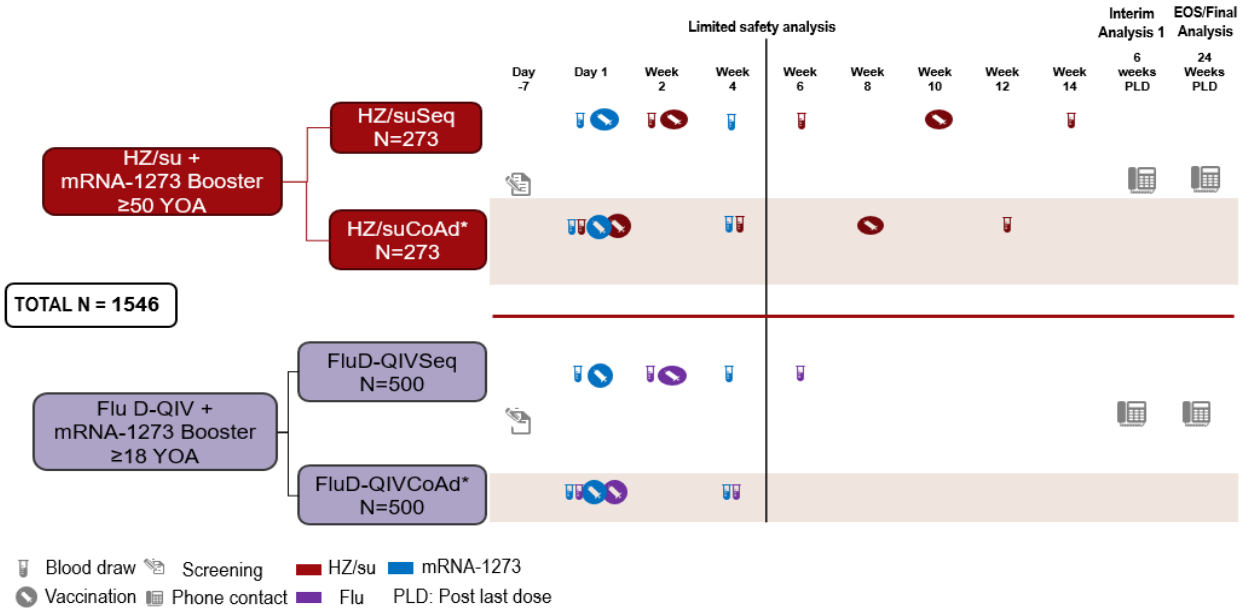
3. Investigational Plan

3.1. Overall Study Design and Plan

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*).

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

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 1).

Table 1 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)***

- 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 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.

3.2. Study Endpoints

Please refer to Section 2 of this SAP.

3.3. Treatments

Table 2 Study interventions administered

Study Intervention Name:	**HZ/su**		**Flu D-QIV**	**mRNA-1273**
Product Name:	VZV gE	AS01B	Flu D-QIV 2021-2022 NH	COVID-19 mRNA Vaccine
Study intervention Formulation:	VZV gE (50 µg)	AS01B: 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.

4. General Statistical Considerations

Data will be displayed in all listings sorted by treatment group and cohort.

Continuous data will be described using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). **Categorical data** will be described using the participant count and percentage for each category.

For the **summary statistics** of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean, Confidence Interval (CI) and median will be displayed to one level of precision greater than the data collected. Standard deviation / standard error will be displayed to two levels of precision greater than the data collected.

When count data are presented, percentages/ratio will be rounded to one decimal place. If count is 0 the percentage will be presented as 0.0%. If percentages are 100%, no decimal will be displayed. CI will be presented to two decimal places for proportion/ratio, wherever applicable. A row denoted "Missing" will be included in count tabulations where specified on the shells to account for dropouts and missing values.

The denominator for all percentages will be the number of participants with non-missing values of corresponding parameter in that treatment group or cohort within the analysis population of interest, unless otherwise specified.

Unless otherwise specified, **baseline** will be defined as the last non-missing evaluation prior to first vaccine administration on Day 1, except the HZ/su and Flu D-QIV baseline immunogenicity in participants in the sequential groups which will have Week 2 as baseline.

Study day: If the event is after the reference start date (date of specified vaccine administration) then the study day will be calculated as assessment date – date of vaccine administration + 1 else if event is prior to the reference start date then it will be calculated as assessment date – date of vaccine.

Calculation regarding antibody concentrations/titers: Antibody values reported as below the lower limit of quantification (LLOQ) will be replaced by 0.5 × LLOQ. Values that are greater than the upper limit of quantification (ULOQ) will be converted to the ULOQ. Missing results will not be imputed.

All statistical analyses will be performed using SAS® software version 9.4 or later.

4.1. Sample Size

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 DQIV-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, see Section 8.1. For the Flu D-QIV and mRNA-1273 booster cohort, success must be achieved for both hypothesis 3 and hypothesis 4; see Section 8.1.

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

4.1.1 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).

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. In such a case, the details of the sample size re-estimation requirements for the HZ/su and mRNA-1273 study cohort will be provided explicitly in a subsequent protocol amendment.

Sample size calculations for the HZ/su and mRNA-1273 booster study cohort can be found in Table 3.

Table 3 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.

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

The non-inferiority of Flu D-QIV using GMTs (hypothesis 3, see Section 8.1) 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, see Section 8.2) will be tested using a sequential approach, meaning, hypothesis 3 and 4 (GMT, Flu D-QIV and mRNA-1273 booster primary endpoint), see Section 8.1, must be tested and non-inferiority of Flu D-QIV and mRNA-1273 booster using GMT ratio must be demonstrated before hypothesis 5 (see Section 8.2) 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 (see Section 8.1) is rejected. 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 Flu D-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, the global power 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 4.

Table 4 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.

4.2. Randomization and Stratification

Within each cohort, participants will be centrally randomized in a 1:1 ratio to 1 of the 2 study groups (sequential or co-administration) and receive a Randomization Number through Interactive Response Tool (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. Randomization will be set to ensure at least 69 participants per group will be assigned to the ≥ 70 YOA stratum in the HZ/su and mRNA-1273 booster cohort and at least 75 participants per group will be targeted for assignment to the ≥ 65 YOA stratum in the Flu D-QIV and mRNA-1273 booster cohort.

4.3. Analysis Set

The analysis sets defined in this study are provided in Table 5. 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 Per-Protocol Set (PPS) will be used for analysis of hypothesis 1 and hypothesis 2, see Section 8.1. 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, see Sections 8.1and 8.2.

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 5 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.

Participants may be eliminated from the PPS in their respective cohort, if at any point during the study up to the last post dose blood sampling time point, they incur a condition that has the capability of altering their immune response (i.e., an intercurrent medical condition (IMC)) or are confirmed to have an alteration of their initial immune status.

5. Participant Disposition

5.1. Disposition

Participant disposition will be summarized using the Enrolled Set. The summary will include the number and percentage, where possible for the following categories: Enrolled Set, screen failure, reasons for screen failure, Randomized Set, reasons for exclusion from Randomized Set to Exposed Set, Exposed Set, exposed to at least one study intervention, exposed to full intervention course, vaccine discontinuation, primary reason for vaccine discontinuation, PPS, Excluded from PPS, reason for exclusion from PPS. completed study, withdrawal from study, and primary reason for withdrawal from study. The analysis will be presented by cohort, group and overall. In addition, the number of participants discontinued by visit (attended/dropout) by reason of discontinuation from study vaccine and reason from withdrawal from study will be presented in a separate table.
Participant disposition data listings will be provided. In addition, the following baseline listings will be provided:

- Informed consent and re-screening
- Inclusion/Exclusion criteria
- Screen Failures

A listing of participants in each analysis set will also be provided.

5.2. Protocol Deviations

Data will be reviewed prior to freezing the database to ensure all deviations leading to analysis set exclusions are captured and categorized in the protocol deviations ADaM dataset. The number of participants with at least one significant protocol deviation (defined as a protocol deviation that affects primary efficacy and/or safety assessments (as applicable), the safety or mental integrity of a subject, or the scientific value of the trial project), will be summarized by deviation category, cohort, group and overall for Randomized set. The significant protocol deviations will be listed by-participant.

6. Demographics and Baseline Characteristics

6.1. Demographics

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]).

The demographics and baseline characteristics data collected on the eCRF will be summarized by cohort, group and overall. Listings of participant demographic and baseline characteristics data will be provided to support the summary tables. Summary statistics will be provided descriptively for the following continuous variables:

- Age (year)

A frequency summary (number and percentage) will be provided by treatment group and overall, for the following categorical variables:

- Age group [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]
- Sex (Male, Female)

  For females,
  - Childbearing potential (Yes/No)
  - Baseline pregnancy test: Urine/Serum (Positive/Negative)
- Race (American Indian or Alaska Native, Asian − Central/South Asian Heritage, Asian - Japanese Heritage, Asian - East Asian Heritage, Asian - South East Asian Heritage, Black or African American, Native Hawaiian or Other Pacific Islander, White - Arabic/North African Heritage, White - White/Caucasian/European Heritage, Other, Unknown)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)

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

6.2. Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.0, which will be up-versioned to future MedDRA dictionaries as they become available during the study.

Participant medical history data including specific details will be presented in a listing.

7. Treatments and Medications

7.1. Prior and Concomitant Medications (CM)/Vaccinations

All medications/vaccinations will be coded according to the World Health Organization (WHO) drug dictionary WHO Drug Global B3 Mar 2021, which will be updated to future versions whenever they become available during the study. Vaccination history eCRF was designed to collect relevant vaccines received prior before the study. Listing of influenza, COVID-19, and HZ vaccine receipt in addition to other non-study vaccines which will be reported on the CM form will be provided.

Concomitant medication/vaccination is defined as any medication and vaccination (other than study vaccinations) ongoing at the time the first dose of study vaccination is administered or taken on or after the first dose of the study vaccination. Concomitant medications will be listed for each Anatomical Therapeutic Chemical (ATC) class level 4 and preferred term (PT) by cohort and group.

7.2. Study Treatments

The schedule and detail of study intervention administration was displayed in Table 6.

Table 6 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.

Study vaccine compliance will be summarized by cohort and group using the Randomized Set. The analysis will be repeated by age strata for the HZ/su and mRNA-1273 Exposed Set and Flu D-QIV and mRNA-1273 Exposed Set, respectively. In all compliance summaries, the number of participants who received mRNA-1273 booster will be reported. For the Flu D-QIV and mRNA-1273 booster cohort, compliance with Flu D-QIV vaccination will be summarized by group. For the HZ/su and mRNA-1273 booster cohort, the summary will present the number and percentage of subjects receiving:

- Both vaccinations of HZ/su;
- First vaccination only for HZ/su.

A listing of each study vaccine exposure and administration will be provided to present data collected on CRF.

8. Immunogenicity Analysis

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.

8.1. Primary Immunogenicity Endpoint

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.

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

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

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

Anti-gE antibody concentrations will be summarized 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), and expressed as a between-group GMC ratio at 1 month post-dose 2 of HZ/su. The geometric mean with 95% CI, geometric standard deviation along with median, minimum, maximum derived from the original data will be presented in the table. The geometric mean and geometric standard deviation calculations will be performed by taking the anti-log of the mean and standard deviation of the log10 transformed concentration data.

For anti-gE at 1 month post-dose 2 of HZ/su, the least square point estimate and its 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 to demonstrate non-inferiority of the HZ/suCoAd vs. HZ/suSeq for the HZ/su immune response. 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.

Anti-gE antibody concentrations at all time points (pre-vaccination, 1 month post-dose 1 and 1 month post-dose 2) will be displayed using reverse cumulative curves.

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

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

Anti-S Protein antibody concentrations will be summarized at pre-vaccination (Day 1) and at 1 month post mRNA-1273 booster dose (at Week 4 for both groups, HZ/suSeq and HZ/suCoAd), and expressed as a between-group GMC ratio at 1 month post mRNA-1273 booster dose. The geometric mean and geometric standard deviation by anti-log10 transformation, along with median, minimum, maximum derived from the original data will be presented in the table.

For anti-S Protein at 1 month post mRNA-1273 booster dose, the least square point estimate and its 95% CI of the between group GMC ratios will be computed using ANCOVA model on the log10 transformation of the concentrations to demonstrate non-inferiority of the HZ/suCoAd vs. HZ/suSeq for the HZ/su immune response. 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.

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

Flu D-QIV immunogenicity (anti-HI antibodies)

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

Anti-HI antibody titers against each of 4 influenza strains included in Flu D-QIV will be summarized at pre-vaccination vaccination (at Day 1 for FluD-QIVCoAd, at Week 2 for FluD-QIVSeq) and at 1 month post Flu D-QIV (at Week 6 for FluD-QIVSeq, at Week 4 for FluD-QIVCoAd), and expressed as a between-group GMT ratio at 1 month post Flu D-QIV. The geometric mean and geometric standard deviation by anti-log10 transformation, along with median, minimum, maximum derived from the original data will be presented in the table.

To demonstrate non-inferiority of the FluD-QIVCoAd vs. FluD-QIVSeq for the Flu D-QIV immune response in terms of anti-HI antibody GMTs, the least square point estimate and its 95% CI of the between-group GMT ratios post-dose 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.

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

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

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

booster dose. The geometric mean and geometric standard deviation by anti-log10 transformation, along with median, minimum, maximum derived from the original data will be presented in the table.

For anti-S Protein at 1 month post mRNA-1273 booster dose, the least square point estimate and its 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 to demonstrate non-inferiority of the FluD-QIVCoAd vs. FluD-QIVSeq for the Flu D-QIV immune response. 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.

8.2. Secondary Immunogenicity Endpoint

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.

8.2.1. Secondary Endpoints for Flu D-QIV immunogenicity (Anti-HI antibody SCRs)

The immunogenicity assessment of the Flu D-QIV secondary endpoint (Hypothesis 5) 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) for the Flu QIV and mRNA-1273 PPS.

To demonstrate non-inferiority of the FluD-QIVCoAd vs. FluD-QIVSeq for the Flu D-QIV immune response 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 DQIV (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).

8.2.2. Descriptive immune endpoints

8.2.2.1 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) at baseline and at 1 month post-dose 2 of HZ/su (at Week 14 for HZ/suSeq, at Week 12 for HZ/suCoAd) for the HZ/su and mRNA-1273 PPS.

- VRR with exact 95% CI at 1 month post-dose 2 of HZ/su
  - The VRR for anti-gE post-dose 2 is defined as the percentage of participants who have at least:
    - 4-fold increase in the post-dose anti-gE antibody concentration as compared to the pre-vaccination anti-gE antibody concentration, for participants who are seropositive at pre-vaccination, or,
    - A 4-fold increase in the post-dose anti-gE antibody concentration as compared to the anti-gE antibody cut-off value of 97 mIU/mL 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 anti-gE antibody concentration is greater than or equal to the assay cutoff 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 at all time points (pre, Dose 1 and Dose 2) will be displayed using reverse cumulative curves.

- MGI in anti-gE antibody 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 enzyme linked immunosorbent assay (ELISA) concentrations.

- The distribution of the fold increase in anti-gE antibody ELISA concentrations 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.

8.2.2.2 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 and ≥ 65 YOA for Flu DQIV 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.

8.2.2.3 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). 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).

- 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 pre-vaccination 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 $\geq 1:40$ or a pre-vaccination titer $\geq 1:10$ 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 $\geq$ 70% in participants aged 18-64 YOA or $\geq$ 60% in participants $\geq$ 65 YOA.

- The lower limit of the 95% confidence interval for SCR should be $\geq$ 40% in participants aged 18-64 YOA or $\geq$ 30% in participants $\geq$ 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.

8.3. Exploratory Immunogenicity Endpoints

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 8.2.2.1. The analysis of this data will use HZ/su and mRNA-1273 PPS.

Neutralizing antibodies for SARS-CoV-2 (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. Summaries will be produced for the HZ/su and mRNA-1273 PPS or

Flu D-QIV and mRNA-1273 PPS depending on the cohort.

Descriptive humoral immune responses to vaccination and/or SARS-CoV-2 infection for anti-RBD protein:

- 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]). Summaries will be produced for the HZ/su and mRNA-1273 PPS or Flu D-QIV and mRNA-1273 PPS depending on the cohort.

Descriptive humoral immune responses to SARS-CoV-2 infection for anti-N:

- 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 postvaccination OR for a participant seropositive at baseline, a 4-fold or more increase post-vaccination. Summaries will be produced for the HZ/su and mRNA1273 Exposed Set or Flu D-QIV and mRNA-1273 Exposed Set depending on the cohort.

9. Safety Analysis

Safety analysis includes solicited AEs, unsolicited AEs, SAEs, pIMDs, AESIs, COVID-19 cases, HZ episodes/cases, pregnancy tests and pregnancy events/outcomes. The safety endpoints will be summarized for each cohort on the HZ/su and mRNA-1273 Exposed Set and on the Flu D-QIV and mRNA-1273 Exposed Set, respectively. PIMDs, and HZ episodes/cases will be summarized on the HZ/su and mRNA-1273 Exposed Set only. All the safety analyses under the secondary objective are descriptive. Subgroup analyses by age strata (as applicable to each study cohort) will be performed.

9.1. Adverse Events

The timeframes for collecting and reporting the safety information are provided in Table 7.

Table 7 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
Unsolicited AEs	Day 1 through Day 30 following each study intervention administration
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

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

9.1.1. Solicited Adverse Events

Solicited AEs are pre-specified local and systemic adverse events. Solicited AEs will be collected through 7 days following each vaccination. Solicited AEs with onset during the 7-day solicitation period that continue beyond the 7-day period will be reported as solicited AEs. The solicited AEs will be collected using the diary eCRFs.

Participant's compliance with respect to the diary card based on the Exposed Set will be determined separately for local and systemic events for the following:

- Number of participants who did not present diary data at all
- Number of participants who completed diary card, regardless of visit
- Number of participants who completed diary card for each day of the first 7 days post any vaccination (i.e., Day 1, Day 2, Day 3, Day 4, Day 5, Day 6 and Day 7)

A sensitivity analysis to exclude participants who may not have acceptable diary data or certain missing diary records may be performed.

A separate listing of PI assessment of solicited AE diary discrepancies will be provided.

Per the study design and diary forms, participants who receive the administration of the mRNA-1273 booster vaccine on Day 1, have until Day 14 (Week 2) to receive the next vaccine administration. As such, all solicited AEs that occurred on or after mRNA-1273 booster vaccine but prior to HZ/su or Flu D-QIV vaccine administration on Day 14 (Week 2) are deemed to be attributable to the mRNA-1273 booster vaccine. For participants in the sequential groups (HZ/suSeq, FluD-QIVSeq), the diary forms are re-set at the time of first

HZ/su or Flu D-QIV vaccination on Day 14 (Week 2) to collect solicited AEs that are either ongoing from mRNA-1273 booster vaccine from Day 1 or occurred on or after the first HZ/su or Flu D-QIV vaccination on Day 14 (Week 2). The diary data is therefore setup to ensure that any solicited AE attributable to each of the following vaccines only: mRNA-1273 booter, first HZ/su, second HZ/su or Flu D-QIV, can be determined depending on the time of the AE relative to the time of each vaccine administration, and prior to the date of any subsequent vaccination.

For data analysis purposes, the CoAd groups (HZ/suCoAd, FluD-QIVCoAd) will be presented as a single column, with the exception of the HZ/suCoAd group that certain selected outputs will be displayed by the first and second HZ/su vaccine doses respectively.

For the sequential groups (HZ/suSeq, FluD-QIVSeq), data will be presented by the individual vaccines as follows:

- A column for mRNA-1273 booster vaccine on Day 1,
- A column for either HZ/su or FluD-QIV vaccine on Day 14 (Week 2) depending on the sequential group,
- A column labelled “Overlapping” to count participants with events that occurred on or after post mRNA booster vaccine dose given at Day 1 and are ongoing after receiving the first HZ/su or Flu D-QIV at Day 14 (Week 2)
- A column labelled either “mRNA-1273 or HZ/su” or “mRNA-1273 or Flu D-QIV” depending on the sequential group, that counts the number of events that each participant experienced under mRNA-1273 or HZ/su vaccine for HZ/SuSeq group or under mRNA-1273 or Flud-QIV vaccine for FluD-QIVSeq group. For participants with overlapping AEs, their events are counted once at maximum severity for any vaccination.

In addition, and specifically for the HZ/su groups (HZ/suSeq, HZ/suCoAd), selected outputs will be displayed by the first and second HZ/su vaccine doses administered within each HZ/suSeq and HZ/suCoAd treatment groups respectively.

The duration of each solicited adverse event will be calculated following the process below:

- the diary data is setup in Study Data Tabulation Model (SDTM) to capture separately events that occurred within the first 7 days and events that occurred longer than 7 days. The 2 datasets are set together.
- Then for each solicited AE that occurred following each vaccination, duration is calculated as sum of the unique number of days of the solicited AE with greater than zero grade

The following specific solicited adverse events will be assessed.
Local solicited AEs:

- Pain
- Redness

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

Systemic solicited AEs:

- Fatigue
- Myalgia
- Headache
- Shivering/chills
- Fever
- Gastrointestinal (GI) symptoms (nausea, vomiting, diarrhea and/or abdominal pain). Each symptom under GI will be presented separately and then collectively as GI. For intensity for GI, the highest intensity among all these 4 symptoms will be used. For example – if a subject experiences grade 1 nausea, grade 2 vomiting, grade 3 diarrhea and grade 2 abdominal pain, then the intensity for GI for the subject will be presented as the highest, i.e., grade 3.
- Arthralgia

The solicited AEs will be MedDRA coded to the following PTs for summaries combining solicited and unsolicited AEs.

Solicited AE	Preferred Term Code	Preferred Term

The number and percentage of participants with at least 1 solicited local event, with at least 1 solicited systemic event and any solicited event as well as each solicited local and solicited systemic AE (within onset within Days 1-7) will be tabulated with exact 95% CIs, for each vaccination visit and overall for all study groups (HZ/suSeq, HZ/suCoAd, FluD-QIVSeq, FluD-QIVCoAd). Similar summaries will be provided for participants with Grade 3 events, medically attended solicited local events, and medically attended solicited systemic events.

The duration in days of the solicited AEs, both local (for each vaccine separately) and systemic, with onset within 7-days following each vaccination visit and overall (total duration) will be calculated and summarized by mean, median, standard deviation, and range. Similar summaries will be provided for participants with Grade 3 events.

In addition, the following below will be presented:

- The percentage of subjects with solicited local adverse events lasting longer than 7 days and duration in days (total) of solicited local adverse events lasting longer than 7 days following each vaccination visit

- The percentage of subjects with solicited systemic adverse events lasting longer than 7 days and duration in days (total) of systemic adverse events lasting longer than 7 days following each vaccination visit

All of the analyses above related to solicited adverse events will be repeated by the age strata within each study cohort. Separate individual data listings for solicited local adverse events and solicited systemic events will be provided. A separate individual data listing of Principal Investigator (PI) assessment of solicited AE diary discrepancies will be provided.

9.1.2. Unsolicited Adverse Events

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.

The number and percentage of participants reporting unsolicited AEs classified by MedDRA primary SOC and 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 summarized by intensity (any grade and Grade 3), any related to study vaccine, Grade 3 related, Grade 3 non-serious, Grade 3 non-serious related, and resulting in a medically-attended visit.

9.1.3. Serious Adverse Events

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

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

pIMDs include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune etiology. See Table 23 of study protocol dated 21September 2021, for a list of potential pIMDs.

The number and percentage of participants reporting pIMDs on the CRF from first vaccination up to 30 days post-last vaccination and from first vaccination up to study end will be summarized for both study groups in the HZ/su and mRNA-1273 booster cohort (HZ/suSeq, HZ/suCoAd, overall). All pIMDs will be summarized by MedDRA SOC and PT. Any related pIMDs will also be summarized for study groups (HZ/suSeq, HZ/suCoAd and overall). pIMDs will be listed.

9.1.5. Adverse events of special interest (AESI)

The number and percentage of participants reporting AESIs on the CRF 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.

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

The number and percentage of participants reporting the following:

- Suspected HZ episodes,
- With at least one lesion sample collected for suspected HZ episode, and
- Confirmed HZ episode

from first dose to study end will be summarized for the HZ/suSeq and HZ/suCoAd study groups. All potential HZ episodes and lesion sampling throughout the entire study period will be listed.

9.1.7. Confirmed HZ episodes (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). The analysis of this data will be restricted to the cases where lesion sample is taken and will follow the suspected HZ episodes discussed in Section 9.1.6.

9.1.8. 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.

Diagnosis and categorization of COVID-19 cases for reporting purposes would 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 $\geq$ 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.

COVID-19 cases by primary case definition, secondary case definition, and tertiary case definition identified on the CRF AE pages will be summarized by number and percentage of participants from first dose to study end for all study groups (HZ/suSeq, HZ/suCoAd, FluD-QIVSeq, FluD-QIVCoAd and overall) and COVID-19 cases will also be listed.

9.1.9. 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 from the notification eCRFs.

9.1.10. 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).

Medical device AE will be recorded on the AE forms as adverse device effect (ADE), serious adverse device effect (SADE) and unanticipated SADE (USADE) and summarized by the number and percent of participants that experience a given event.

10. Safety analysis for Safety Review Team review

The safety review team (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. PPD preclarus dashboard will also be used to generate the required outputs for SRT review

to help decide on continuation of enrollment in the co-administration groups. Periodic analyses will be done for regular SRT review. All SRT analyses will be descriptive.

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. The outputs selected for limited safety analyses will be programmed as TFL outputs using SAS® software version 9.4 or later.

11. Interim Analysis

One formal interim analysis of safety, reactogenicity, and immunogenicity is planned. 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 interim analysis 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. The 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 coadministered with Flu D-QIV).
- Solicited AE 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.

Hypothesis testing at the first analysis will occur in parallel independently 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 interim immunogenicity 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 interim analysis. See Section 4.1 for Type I error adjustments.

The final analysis will include safety follow-up up to 6 months post the last vaccine dose.

12. Changes in the Planned Analysis

No changes from planned analysis.

13. References

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14. Appendices

14.1. Schedule of Activities

See Table 1 of study protocol.