CLINICAL STUDY PROTOCOL

Primary study intervention(s)	BIO FLU SV MRNA (GSK4382276A)
Other study intervention(s)	GSK's Flu Dresden – Quadrivalent Influenza Vaccine Sanofi's Fluzone High-Dose Quadrivalent Vaccine GSK's Flu Dresden – Influenza Vaccine Sanofi's Fluzone High-Dose Vaccine
Study identifier	222853
Abbreviated title	FLU SV MRNA-024
Approval date	24 Sep 2024
Title	A phase 2a randomized, observer-blind, dose-finding study to evaluate the immunogenicity and safety of mRNA-based multivalent seasonal influenza vaccine candidates in adults 18 years of age and older
Brief title	A study to find the dose and assess the immune response and safety of a vaccine against influenza in adults 18 years of age and older
Sponsor	GlaxoSmithKline Biologicals SA Rue de l'Institut 89 1330 Rixensart Belgium
Sponsor signatory	Pascal Peeters, MD Senior Director, Clinical Project Lead

Medical monitor name and contact information can be found in the local study contact information document.

Based on TMF-14732712 Protocol v3.0.

PROTOCOL AMENDMENT 2 INVESTIGATOR AGREEMENT

- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of and will comply with GCP and all applicable regulatory requirements.
- That I will comply with the terms of the clinical study site agreement.
- To ensure that all persons assisting me with the study are adequately informed about the GSK study intervention and other study-related duties and functions as described in the protocol.
- To cooperate with representative(s) of GSK in the monitoring and data management processes of the study with respect to data entry and resolution of queries about the data.

Study identifier	222853
Abbreviated title	FLU SV MRNA-024
Approval date	24 Sep 2024
Title	A phase 2a randomized, observer-blind, dose-finding study to evaluate the immunogenicity and safety of mRNA-based multivalent seasonal influenza vaccine candidates in adults 18 years of age and older
Investigator name	_____
Signature	_____
Date of signature **(DD Month YYYY)**	

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 2	24 Sep 2024
Amendment 1	16 May 2024
Original Protocol	21 Mar 2024

Amendment 2 (24 Sep 2024)

Overall rationale for the current Amendment:

Available clinical immunogenicity and reactogenicity data from studies FLU SV MRNA-002 and FLU SV MRNA-024 have identified CCI [redacted] CCI [redacted] CCI [redacted] (see Section 4.3 for more details on the justification for the selected dose formulation).

The objective of protocol amendment 2 is to consolidate the immunogenicity and reactogenicity data package for this formulation in both age groups CCI [redacted] CCI [redacted]

LIST OF MAIN CHANGES IN THE PROTOCOL AND THEIR RATIONALE:

Section # and title	Description of change	Brief rationale
Throughout the protocol	CCI [redacted] CCI [redacted] CCI [redacted] Relevant protocol sections were revised (as listed below).	To consolidate the immunogenicity and reactogenicity data package with the CCI [redacted] CCI [redacted] CCI [redacted]
2.1. Study rationale 4.1. Overall design 4.2. Scientific rationale for study design 4.3. Justification for dose	Provided updated rationale and study design for protocol amendment 2.	To support protocol amendment 2 study design.
1.2. Schema 4.1. Overall design (Table 5) 6.1. Study intervention(s) administered (Table 6) 8.2.3. Immunological read-outs (Table 9)	Addition of one new investigational study intervention dose formulation per age group and corresponding age-appropriate comparators. Number of participants updated (approximately 320 new participants to be enrolled; 160 younger adults and 160 older adults). Tables 5 and 6 were updated to include details of study interventions used in protocol amendment 2.	To align with protocol amendment 2 study design.

Section # and title	Description of change	Brief rationale
	Table 9 was updated to include additional participants in the study (total number of participants changed from 500 to 820; number of participants in a subset changed from 250 to 410).	
9.4.1. Sequence of interim analyses and other planned analyses 9.5 Sample size determination (including Tables 16 and 17)	Updated to include groups receiving the additional dose formulation and comparators in the statistical analysis.	To align with protocol amendment 2 study design.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADE	Adverse device effect
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
CA	Competent authority
CFR	Code of Federal Regulations
CONSORT	Consolidated standards of reporting trials
CSR	Clinical study report
ECG	Electrocardiogram
eCRF	Electronic case report form
eDiary	electronic Diary
CCI [redacted]	
EoS	End-of-study
FDA	Food and Drug Administration
FSFV	First subject first visit
FSH	Follicle stimulating hormone
GBS	Guillain-Barré Syndrome
GCP	Good clinical practices
GDPR	General data protection regulation
HA	Hemagglutinin
CCI [redacted]	
HIPAA	Health Insurance Portability and Accountability Act
HLT	High-level term
HRT	Hormonal replacement therapy
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council on Harmonization
ICSR	Individual case safety reports
IEC	Independent Ethics Committee
IM	Intramuscular
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional review board
iSRC	Internal Safety Review Committee
LSLV	Last subject last visit
MAAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MN	Microneutralization
MRI	Magnetic resonance imaging
CCI [redacted]	
NH	Northern Hemisphere
CCI [redacted]	

Abbreviation	Definition
PCA	Primary completion analysis
PI	Personal information
pIMD	Potential immune-mediated diseases
PT	Preferred term
QTL	Quality tolerance limit
RNA	Ribonucleic acid
RTSM	Randomization and Trial Supply Management
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical analysis plan
SmPC	Summary of product characteristics
SoA	Schedule of activities
SoC	Standard of care
SRT	Safety review team
SUSAR	Suspected unexpected serious adverse reaction
TOC	Table of contents
ULN	Upper limit of normal
USADE	Unanticipated serious adverse device effect
WHO	World Health Organization
WOCBP	Woman of childbearing potential
WONCBP	Woman of non-childbearing potential

Term	Definition
Blinding	A procedure in which 1 or more parties to the study are kept unaware of the intervention assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the study, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a SAE. In an observer-blind study, the participant, the site, and sponsor personnel involved in the clinical evaluation of the participants are blinded while other study personnel may be aware of the treatment assignment.
Caregiver	A "caregiver" is someone who: • lives in the close surroundings of a participant and has a continuous caring role or • has substantial periods of contact with a participant and is engaged in their daily health care (e.g., a relative of the participant, a nurse who helps with daily activities in case of residence in a nursing home). In the context of a clinical study, a caregiver could include an individual appointed to oversee and support the participant's compliance with protocol-specified procedures.
Certified copy	A copy (irrespective of the type of media used) of the original record that has been verified (e.g., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.
Combination product	Combination product comprises any combination of: • drug • device • biological product.

Term	Definition
	Each drug, device and biological product included in a combination product is a constituent part.
Comparator	Any product used as a reference (including placebo, marketed product, GSK, or non-GSK) for an investigational product being tested in a clinical trial. This is any product that is being used to assess the safety, efficacy, or other measurable value against the test product (IMP).
eDiary	Electronically recorded patient data and automated data entries on, for example, a handheld mobile device, tablet, or computer.
Eligible	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Essential documents	Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.
Intercurrent event	Event occurring after study intervention initiation that affects either the interpretation or the existence of the measurements associated with the clinical question of interest.
Intervention number	A number identifying the intervention assigned to a participant, according to intervention allocation.
IMP	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.
Invasive medical device	A device which, in whole or in part, penetrates inside the body, either through a body orifice or throughout the surface of the body.
Investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate study-related duties and functions conducted at the study site to qualified individual or party to perform those study-related duties and functions.
LSLV	The date on which the last participant in a clinical study was examined or received an intervention/treatment to collect final data for the primary outcome measures, secondary outcome measures, and AEs (that is, the last participant's last visit or LSLV).
Medicinal products used to assess endpoints	A product given to the participant in a clinical trial as a tool to assess a relevant clinical trial endpoint; it is not being tested or used as a reference in the clinical trial.
Participant	Term used throughout the protocol to denote an individual who has been contacted to participate or who participates in the clinical study as a recipient of the study intervention (vaccine(s)/product(s)/comparator). Synonym: subject.
Participant identifier	A unique identification number assigned to each participant who consents to participate in the study.
Placebo	An inactive substance or treatment that looks the same as, and is given in the same way as, an active drug or intervention/treatment being studied.
Primary completion date	This is the date that the final participant in the study was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated. In other words, Primary Completion Achieved is the date of the last contact with the participant when data has been collected/intervention done for the purpose of data collection for analysis of all primary endpoints. In the case of clinical studies with more than 1 primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes. This date may occur prior to the study end or be the same date as the study end milestone.

Term	Definition
Randomization	Process of random attribution of intervention to participants to reduce selection bias.
Self-contained study	Study with objectives not linked to the data of another study.
Source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
Standard of care	Medicine(s) for a specific indication, or a component of the standard care for a particular medical indication, based on national and/or international consensus; there is no regulatory significance to this term. Products/regimens considered standard of care may differ country to country, depending on consensus in individual countries.
Study intervention	Term used throughout the clinical study to cover all types of investigational and non-investigational products including medical devices and vaccines intended to be administered to the study participants during the study conduct. Procedures conducted to manage participants or to collect data are excluded from the usage of this term.
Study monitor	An individual assigned by the sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.
Subset	A group of participants for whom specific assessments are planned as compared to other participants or a group of participants who share a common characteristic (e.g., age, vaccination schedule, etc.) at the time of enrollment.
SUSAR	In a clinical trial, a serious adverse reaction that is considered unexpected, i.e., the nature or severity of which is not consistent with the reference safety information (e.g., IB for an unapproved IMP). All ADRs that are both serious and unexpected are subject to expedited reporting.

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol title: A phase 2a randomized, observer-blind, dose-finding study to evaluate the immunogenicity and safety of mRNA-based multivalent seasonal influenza vaccine candidates in adults 18 years of age and older.

Brief title: A study to find the dose and assess the immune response and safety of a vaccine against influenza in adults 18 years of age and older.

Rationale: This Phase 2a study is a dose-finding study investigating CCI

CCI

Objectives, endpoints, and estimands: The primary and key secondary objectives focus on the evaluation of humoral immune response induced by the investigational study intervention, as well as its safety and reactogenicity profile. For the full list of objectives, endpoints, and estimands refer to Section 3.

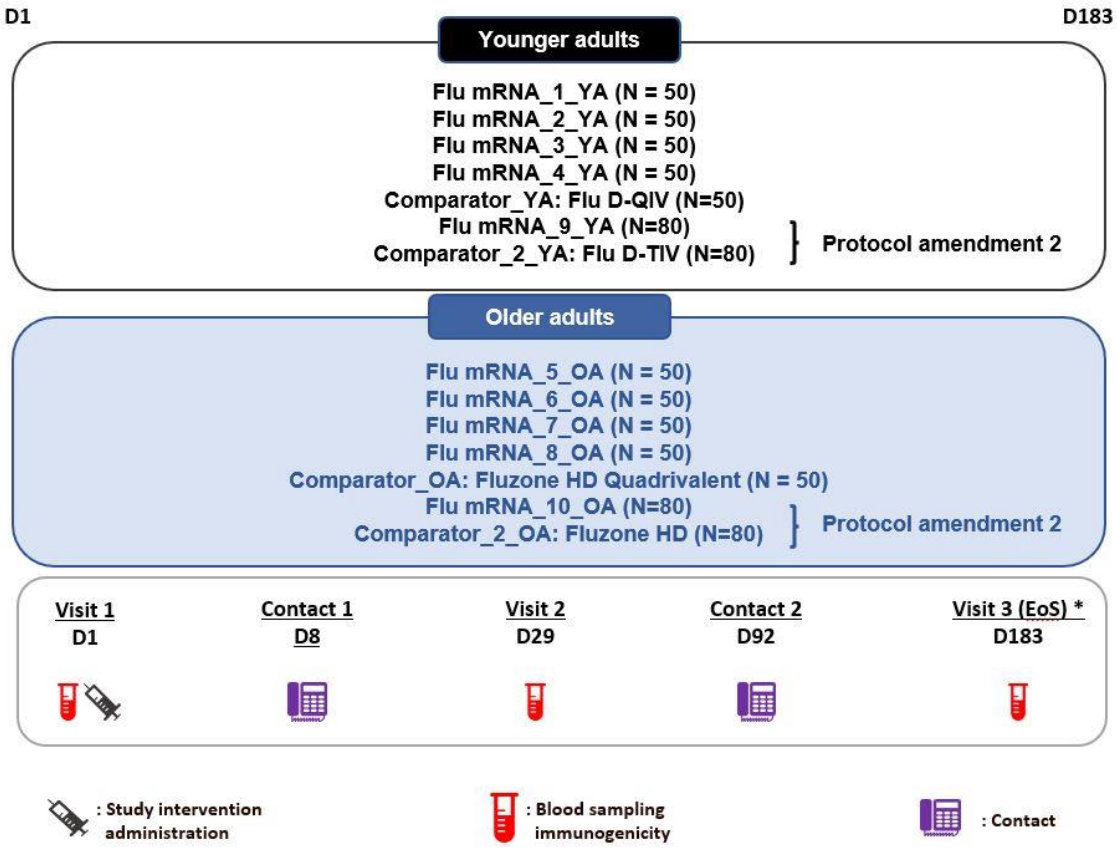
Overall design: This is an observer-blind study conducted in healthy or medically stable participants 18-64 (younger adults, YA) and 65-85 (older adults, OA) years of age. Participants will be enrolled in parallel to 4 Flu mRNA groups and 1 comparator group per age category in the initial part of the study or 1 Flu mRNA group and 1 comparator group per age category in protocol amendment 2. For details refer to Section 4.1.

Number of participants: Planned (approximate) number of participants to be enrolled: 250 YAs (50 participants per group) and 250 OAs (50 participants per group) in the initial part of the study, and 160 YAs (80 participants per group) and 160 OAs (80 participants per group) in protocol amendment 2. For details refer to Section 9.5.

Data monitoring/other committee: A blinded Safety Review Team (SRT) will review available safety data on a regular basis throughout the study. If a potential safety concern/signal is identified that requires unblinded review, an unblinded internal Safety Review Committee (iSRC), independent from the project, will review available safety data. For details refer to Section 10.1.6.

1.2. Schema

Figure 1 Study design overview



D: day; N: number of participants;
*Visit 3 will be replaced by a contact if participant has received the standard of care (SoC) vaccination against seasonal flu after Visit 2 and prior to this visit and did not report any adverse events that would require physical examination on site.

1.3. Schedule of activities

Table 1 Schedule of activities

Type of contact	Visit 1	Contact 1	Visit 2	Contact 2	Visit 3[1]	Notes
Timepoints	**Day 1**	**Day 8**	**Day 29**	**Day 92**	**Day 183**	
Informed consent	●[2]					See Section 10.1.3 for more information.
Inclusion and exclusion criteria	●[2]					See Section 5.1 and Section 5.2 for Inclusion and Exclusion criteria.
Check with participant if they will appoint a caregiver and distribute information letter(s) to caregiver, when applicable	○[2]					See Section 8 for more information.
Collect demographic data	●[2]					See Section 8.1.1 for more information.
Collect medical history	●[2]					See Section 8.1.2 for more information.
Collect influenza vaccination history over the past 2 years	●[2]					See Section 8.1.2 for more information.
Physical examination	●[2]		○		○	Physical examination after Day 1 will be performed only if the participant indicates that there might be some underlying pathology(ies) or if deemed necessary by the investigator or delegate. See Section 8.3.1 for more information.
Study intervention						
Check criteria for temporary delay of study intervention administration[3]	●[2]					See Section 5.5 for more information.
Check contraindications, warnings, and precautions to vaccination	●[2]					See Section 8.3.3 for more information.
Body temperature before study intervention administration	●[2]					Fever is defined as a temperature ≥38.0°C/100.4°F regardless the location of measurement. The preferred location for measuring temperature will be the oral cavity.
Urine pregnancy test (only for female participants of childbearing potential)	●[2]					See Section 8.3.5 for more information.
Randomization and intervention number allocation	●[2]					Participants will be randomized between study groups at an equal ratio using a stratified permuted block randomization with age group, country, and previous flu vaccination in the preceding 2 years as stratification factors. See Section 6.3 for more information.

Type of contact Timepoints	Visit 1 Day 1	Contact 1 Day 8	Visit 2 Day 29	Contact 2 Day 92	Visit 3[1] Day 183	Notes
Administration of study intervention	●					See Section 6.1 for more information.
Recording of administered study intervention number	●					See Section 6.5 for more information.
Distribution of "Participant card"	○					See Section 8.4.8 for more information.
Check participant's device compatibility for eDiary data collection	○					See Section 8.1.3 for more information.
Training and installing[4]/assigning of eDiaries	○					See Section 10.3.5.1 for more information.
Review of the eDiary data by site staff	○	○	○			If solicited events are ongoing on and beyond Day 29, they will be followed up using eDiary until resolution. See Section 10.3.5.1 for more information.
Returning/uninstalling[4] of eDiaries			○			Participants with solicited events ongoing at Visit 2 will return the eDiary or uninstall the eDiary app after Visit 2, once the event has resolved. See Section 10.3.5.1 for more information.
Laboratory assessment						
Blood sampling for humoral immunogenicity assessments (approximately 15 mL)	○[2,5,6]		○[5]		○[5,7]	See Section 8.2.1 for more information.
Safety assessments						
Record concomitant medications/vaccinations	●	●	●	●	●	See Section 6.9 for more information.
Record intercurrent medical conditions	●	●	●	●	●	See Table 11 for details about time period for recording intercurrent medical conditions.
Recording of solicited events (Days 1–7 post-dosing)	○[8,9]					See Table 11 for details about time period for collecting solicited events and Section 10.3.3 for more information. Solicited events ongoing at the end of solicited period (Day 1-Day 7) are to be followed up until resolution.
Recording of unsolicited AEs (Days 1-28 post-dosing)	●	●				See Table 11 for details about time period for collecting unsolicited AEs and Section 10.3.4 for more information.
Recording of MAAEs, AESIs, SAEs and AEs leading to withdrawal from study	●	●	●	●	●	See Table 11 for details about time period for collecting safety information and Section 10.3.5 for more information.
Recording of pregnancies	●	●	●	●	●	See Section 10.3.5 for more information.

Type of contact	Visit 1	Contact 1	Visit 2	Contact 2	Visit 3[1]	Notes
Timepoints	**Day 1**	**Day 8**	**Day 29**	**Day 92**	**Day 183**	
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●	●	●	Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study. See Table 11 for details about time period for collecting safety information and Section 10.3.5 for more information.
Study conclusion					●	

AE: adverse event; AESI: adverse event of special interest; MAAE: medically attended adverse event; SAE: serious adverse event.

Note: The double-line border following Day 29 indicates the analyses which will be performed on all data (i.e., data that are as clean as possible) for primary and secondary endpoints obtained up to Day 29.

Contact may be via telephone, SMS, email, video-telephone/telemedicine or other means, depending on local best practice.

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

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

[1] Visit 3 (Day 183) will be replaced by a contact if participant has received the standard of care vaccination against seasonal flu after Visit 2 and prior to this visit and did not report any AEs that would require physical examination on site.

[2] Is used to indicate a study procedure to be performed prior to study intervention administration.

[3] If the study intervention administration is delayed for any reason, the following procedures should be performed on the day of study intervention administration: physical examination, body temperature measurement, urine pregnancy test, check for contraindications, warnings, and precautions to vaccination, and blood sample collection (the first blood sample will be destroyed if taken at an earlier time).

[4] For participants who will bring their own device.

[5] Is used to indicate a sample collection procedure that requires documentation in the validated digital collection application for samples management.

[6] Criteria for temporary delay for study intervention administration to be checked prior to taking blood sample.

[7] Blood samples should only be collected for participants who did not receive a SoC vaccination against seasonal flu after Visit 2 and prior to this visit.

[8] Is used to indicate a study procedure recorded in eDiary.

[9] Solicited events will be recorded in eCRF by sites, only when participant missed to record the event in eDiary.

Table 2 Intervals between study visits

Interval[1]	Planned visit interval	Allowed interval range
Visit 1[2] → Contact 1	7 days	7-10 days
Visit 1[2] → Visit 2	28 days	28-35 days
Visit 1[2] → Contact 2	91 days	77-105 days
Visit 1[2] → Visit 3[3]	182 days	180-210 days

[1] Interval is computed as the difference between 2 dates.
[2] Visit 1 corresponds to the day of the study intervention administration. If the study intervention administration date is different from the ICF signature date, the study intervention administration date needs to be taken as a reference for calculating intervals relative to subsequent visits.
[3] Visit 3 will be replaced by a contact if participant has received the standard of care vaccination against seasonal flu after Visit 2 and prior to this visit and did not report any AE that would require physical examination on site.

2. INTRODUCTION

2.1. Study rationale

The purpose of this Phase 2a study is to evaluate the immunogenicity and safety of the CCI seasonal influenza investigational study interventions. The study follows a Phase 1/2 study (FLU SV MRNA-002) that investigated CCI CCI CCI. In the current Phase 2a study, investigational study interventions CCI CCI will be investigated to explore possible ways to CCI

Available clinical immunogenicity and reactogenicity data from this study and study FLU SV MRNA-002 have CCI CCI CCI CCI

The objective of protocol amendment 2 is to consolidate the immunogenicity and reactogenicity data package for this formulation in both age groups CCI CCI

See Section 4.3 for more details on the justification of the selected dose formulation.

2.2. Background

Influenza is an infectious disease caused by influenza viruses, enveloped negative-sense RNA viruses belonging to the Orthomyxoviridae family. Four types of influenza viruses have been identified, of which type A and B are primarily responsible for human disease.

Influenza causes variable but often high rates of seasonal disease in the human population, with consequent significant morbidity and mortality. Uncomplicated influenza is characterized by the abrupt onset of general and respiratory symptoms which usually resolve within a week. However, in vulnerable populations such as the elderly

and young children, influenza can aggravate existing medical conditions and potentially lead to life-threatening complications. During seasonal epidemics, 5-15% of the world's population is typically infected, resulting in 3-5 million cases of severe illness. Moreover, up to 650 000 deaths annually are associated with seasonal influenza [WHO, 2023a].

Annual influenza vaccination is currently the most effective strategy for controlling influenza and preventing its associated respiratory and non-respiratory complications and mortality [WHO, 2023a]. However, the effectiveness of influenza vaccines has historically been suboptimal, ranging from as little as 10% in years when vaccine and circulating strains are mismatched, to a maximum of 60% (2004 to 2023 influenza seasons in the United States [US]) [CDC, 2023].

Several parameters contribute to the limitations in terms of effectiveness and availability of the currently licensed influenza vaccines and use of new technologies may be needed to improve the immunogenicity of influenza vaccines. The mRNA technology has key attributes that can be leveraged to overcome the limitations of the currently licensed influenza vaccines including avoiding egg-adaptation mutations, rapid, and scalable manufacturing process, and facilitating multicomponent vaccine formulations. GSK ***is*** developing a seasonal influenza vaccine based on mRNAs encoding influenza HA CCI [redacted], encapsulated in lipid nanoparticles.

Please refer to the current Investigator's Brochure (IB) for information regarding pre-clinical and clinical studies of Flu Seasonal mRNA.

2.3. Benefit-risk assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of Flu Seasonal mRNA investigational study intervention may be found in the IB.

Detailed information about the known and expected benefits and risks and expected AEs related to the licensed influenza vaccines used as comparators can be found in the respective Summary of Product Characteristics (SmPC) or Prescribing Information.

As for any vaccine, administration site (e.g., pain, swelling, erythema) and systemic (e.g., fever, fatigue, headache, myalgia) post-dosing events may occur within the first week of study intervention administration, and are anticipated to resolve within a few days of onset.

2.3.1. Risk assessment

Potential risk of clinical significance	Summary of data/Rationale for risk	Mitigation strategy
All study vaccines		
Hypersensitivity reactions, including anaphylaxis	Hypersensitivity reactions following vaccinations are not uncommon but are mostly nonserious. Serious allergic reactions, including anaphylaxis, are usually very rare [McNeil, 2019]. In a Vaccine Safety Datalink (VSD) study, the estimated incidence of anaphylaxis was 1.3 per million vaccine doses administered for all vaccines and 1.6 per million doses for trivalent influenza vaccine [McNeil, 2019]. The US VSD found that most cases of anaphylaxis occurred shortly after vaccination [Law, 2021]. In general, the symptoms can be treated successfully if the treatment is started quickly. There is currently limited data on the risk of hypersensitivity reactions following mRNA influenza vaccines. The US Centers for Disease Control and Prevention (CDC) noted the reporting rate of anaphylaxis following mRNA Covid-19 vaccines to be 2.5 to 4.7 cases/million doses administered [Shimabukuro, 2021].	Severe hypersensitivity events occurring within 24 hours of dosing will be collected as AESIs. Participants with a history of hypersensitivity to any previous vaccine or any component of the study intervention (including polyethylene glycol, egg protein and aminoglycoside antibiotics) will be excluded from study participation. All participants will be observed for 30 minutes after dosing. Appropriate resuscitation equipment, medication and trained staff will be available at the vaccination site. Participants will be instructed to contact the study site immediately for occurrence of any possible hypersensitivity reaction within 1 day following study intervention administration.
Bell's Palsy	Previous studies have shown controversial results on the risk of Bell's palsy after influenza vaccination [Ozonoff, 2021; Bardage, 2011; Huang, 2012; Wijnans, 2017; Baxter, 2017; Mutsch, 2004]. A review of vaccine adverse event reporting system (VAERS) data found increased reporting of facial paralysis following any influenza vaccination seems to be higher compared with that following the administration of other vaccines. However, the authors cautioned that the findings need to be interpreted in light of the limitations of data generated from VAERS, which is exploratory rather than confirmatory [Kamath, 2020]. A recent review of vaccines, including influenza vaccines and mRNA-based Covid-19 vaccines, and Bell's palsy found insufficient evidence to confirm an excess risk of Bell's palsy following	Participants with a history of Bell's palsy, will be excluded from the study enrollment. Moreover, pIMDs including Bell's palsy will be collected as AESIs.

Potential risk of clinical significance	Summary of data/Rationale for risk	Mitigation strategy
	vaccination, with the exception of an intranasally administered influenza vaccine adjuvanted with *E.coli* heat-labile toxin. In the case of the intranasal influenza vaccine, the adjuvant was the suggested cause [Bertin, 2022]. Literature is sparse regarding the potential mechanism that may be involved. Of note, Bell's palsy has also been reported to occur following influenza infection. Bell's palsy is included in the product information (under Post-Marketing Data) of some influenza vaccines (e.g., *Fluzone Quadrivalent*, *Fluzone High-Dose Quadrivalent*). Given the association between influenza infection and the incidence of facial palsy and due to the earlier associations with influenza vaccination and that the potential mechanism is still not completely understood, Bell's palsy is proposed as an important potential risk for this candidate vaccine.	
Guillain-Barré Syndrome (GBS)	An association between GBS and influenza vaccination was initially suggested during the 1976–1977 swine flu immunization campaign [Langmuir, 1984; Schonberger, 1979]. A meta-analysis of 39 studies published between 1981 to 2014 found a marginally statistically significant increased risk of GBS for seasonal flu vaccines (RR=1.22; 95% CI, 1.01-1.48) [Martin Arias, 2015]. However, the CDC notes that the data on the association between GBS and seasonal flu vaccination are variable and inconsistent across flu seasons. If there is an increased risk of GBS following flu vaccination it is small, in the order of 1 to 2 additional GBS cases per million doses of flu vaccine administered [CDC, 2015]. The risk window of GBS is in the first 6 weeks post-vaccination. One of the biological mechanisms for GBS following influenza vaccine may involve the synergistic effects of endotoxins and vaccine-induced autoimmunity. Of note, influenza infection has also been associated with	Participants with a history of GBS, will be excluded from the study enrollment. Moreover, pIMDs including GBS will be collected as AESIs

Potential risk of clinical significance	Summary of data/Rationale for risk	Mitigation strategy
	GBS. The estimated risk of GBS after influenza has been reported to be 17.2 cases per 1 million patients hospitalized with influenza [Babazadeh, 2019]. A recent systematic review and meta-analysis has not found an association between GBS and mRNA Covid-19 vaccines [Ogunjimi, 2023]. GBS has been included in the product information (under Warnings and Precautions and/or Post-Marketing Data) of some influenza vaccines (e.g., *Fluarix Quadrivalent, Fluad Tetra, Fluzone Quadrivalent, Fluzone High-Dose Quadrivalent*). Given the association between influenza infection and GBS and due to the earlier associations with influenza vaccination this potential risk needs to be evaluated for any possible association with the Flu Seasonal mRNA vaccine.	
Study procedures		
Pain and bruising	Pain or bruising at the site where blood is drawn.	A topical analgesic may be applied to the site where blood will be taken.
Syncope and vasovagal reactions to study intervention administration	Syncope (fainting) and other anxiety related reactions can occur as a psychogenic response to the needle injection following or before blood draw or dosing.	To minimize the risk of injury associated with syncope before/after dosing or blood draw, all participants will be seated or lying down during study intervention administration/blood draw and will remain under observation for 30 minutes after the procedure. The decision to dose the participant will be dependent on the clinical judgment of the investigator.
Bleeding following intramuscular injection	As with other intramuscular injections, study intervention should be given with caution in individuals with bleeding disorders, such as hemophilia or on anticoagulant therapy, to avoid the risk of hematoma following the injection.	To minimize the risk of bleeding, study intervention should be given with caution in individuals with thrombocytopenia or any coagulation disorder. Participants with any medical condition that in the judgment of the investigator would make intramuscular injection unsafe will be excluded from study enrollment.

AESIs: Adverse Events of Special interest; CI: Confidence Interval; GBS: Guillain-Barré Syndrome; mRNA: messenger ribonucleic acid; pIMDs: potential Immune-mediated diseases; VAERS: Vaccine Adverse Event Reporting System; VSD: Vaccine Safety Datalink.

2.3.2. Benefit assessment

The participants receiving the Flu Seasonal mRNA investigational study intervention may not directly benefit from this vaccination because vaccine efficacy has not been assessed.

Participants may gain information and medical advice about their general health status through medical evaluations/assessments associated with this study (i.e., physical examinations).

2.3.3. Overall benefit-risk conclusion

The Flu Seasonal mRNA investigational study intervention is currently in an early stage of clinical development. Taking into account the measures taken to minimize risk to participants from this study and given the accumulation of favorable safety/immunogenicity data from the FLU SV MRNA-003 (217895) and the FLU SV MRNA-002 (217884) studies, the potential risks identified in association with the Flu Seasonal mRNA investigational vaccine candidates are justified by the anticipated benefits that may be afforded to study participants. Refer to the IB for more information.

3. OBJECTIVES, ENDPOINTS AND ESTIMANDS

Table 3 Objectives and endpoints

Objectives	Endpoints[1]
Primary	
To evaluate the humoral immune response induced by the investigational study intervention	• CCI titer at Day 29 • Fold increase in CCI titer from Day 1 to Day 29 • CCI seroconversion from Day 1 to Day 29 • CCI at Day 1 and Day 29
Secondary	
To evaluate the humoral immune response induced by the investigational study intervention	In a subset[3] of participants: CCI
To evaluate the safety and reactogenicity profile of the investigational study intervention	• Occurrence of solicited administration site and systemic events within 7 days (i.e., from Day 1 to Day 7) after study intervention administration[4] • Occurrence of unsolicited AEs within 28 days (i.e., from Day 1 to Day 28) after study intervention administration[4] • Occurrence of SAEs[4] within 6 months (i.e., from Day 1 to Day 183) after study intervention administration • Occurrence of AESIs[4] within 6 months (i.e., from Day 1 to Day 183) after study intervention administration • Occurrence of MAAEs[4] within 6 months (i.e., from Day 1 to Day 183) after study intervention administration

Objectives	Endpoints[1]
Tertiary	
CCI [redacted]	

Endpoints are designed for all the participants, unless indicated otherwise in the table.
AE: adverse event; AESI: adverse event of special interest; CCI [redacted]; MAAE: medically attended adverse event; MN: microneutralization; CCI [redacted]; SAE: serious adverse event.
[1] Refer to Table 4 for details of primary and secondary estimands.
[2] For all CCI [redacted] used to design the investigational study interventions.
[3] Refer to Section 4.1 for the description of subset.
[4] Refer to Section 8.3 for the list of safety events and timeframe for collection.

Table 4 Study estimands

Ref #	Population	Objectives	Variable (Endpoint)	Intercurrent event (ICE)[1]		Population level summary
				Description	Handling strategy	
Primary						
1	Younger adults 18-64 YOA and older adults 65-85 YOA	To evaluate the humoral immune response induced by the investigational study intervention	• CCI titer at Day 29 • Fold increase in CCI titer from Day 1 to Day 29 • CCI seroconversion from Day 1 to Day 29 • CCI at Day 1 and Day 29	a) Vaccination administration errors. b) Taken prohibited medication or vaccination prior to Day 29 blood draw. c) Day 29 blood draw taken out of allowed window[3]. d) Medical condition forbidden by protocol (i.e., either a confirmed immunodeficiency condition, new malignancy, or development of confirmed influenza disease) prior to Day 29 blood draw	Hypothetical strategy: data from participant after ICE will be excluded from the analysis.	• Between-group geometric mean titer (GMT) ratio (Flu mRNA candidate over Comparator) with 95% confidence interval (CI) • Within-group geometric mean increase (GMI) with 95% CI • Between-group difference in seroconversion rate (SCR[4]) (Flu mRNA candidate minus Comparator) with 95% CI • Between-group difference in CCI CCI (Flu mRNA candidate minus Comparator) with 95% CI
	Secondary					
2	Refer to 1	To evaluate the humoral immune response induced by the investigational study intervention	CCI	Refer to 1	Refer to 1	Refer to 1

Ref #	Population	Objectives	Variable (Endpoint)	Intercurrent event (ICE)[1]		Population level summary
				Description	Handling strategy	
3	Refer to 1	To evaluate the safety and reactogenicity profile of the investigational study intervention	• Occurrence of solicited administration site and systemic events within 7 days (i.e., from Day 1 to Day 7) after study intervention administration • Occurrence of unsolicited AEs within 28 days (i.e., from Day 1 to Day 28) after study intervention administration • Occurrence of SAEs within 6 months (i.e., from Day 1 to Day 183) after study intervention administration • Occurrence of AESIs within 6 months (i.e., from Day 1 to Day 183) after study intervention administration • Occurrence of MAAEs within 6 months (i.e., from Day 1 to Day 183) after study intervention administration	Not applicable	Treatment policy: all data collected will be included in summaries.	Proportion of participants who report each of the endpoint. No treatment comparison is planned.

Endpoints are designed for all the participants, unless indicated otherwise in the table.

AE: adverse event; AESI: adverse event of special interest; CI: confidence interval; GMI: mean geometric increase; GMT: geometric mean titer; CCI [redacted] ICE: intercurrent event; MAAE: medically attended adverse event; CCI [redacted] SAE: serious adverse event; SCR: seroconversion rate; CCI [redacted] YOA: years of age.

[1] Refer to Section 9.2 for more information on intercurrent events.

[2] All CCI [redacted] used to design the investigational study intervention.

[3] Study discontinuation, blood sample taken out of window and missing result at pre- or post-dose are not considered intercurrent events and will be handled as missing data. More details will be provided in the statistical analysis plan (SAP).

[4] Refer to Section 9.3.1 for definition of SCR and CCI [redacted]

[5] Refer to Section 4.1 for the description of subset.

4. STUDY DESIGN

4.1. Overall design

Refer to Figure 1 (Section 1.2) for the overview of study design.

- Study phase: 2a.
- Single-country, multi-center.
- Self-contained.
- Study population: Healthy or medically stable participants aged 18-64 and 65-85 years of age (Refer to Section 5 for full description of study population).
- Study interventions: single-dose intramuscular (IM) administration of the investigational study intervention or the comparator.
- Comparator: age-appropriate licensed influenza vaccine.
  - GSK's Flu Dresden-Quadrivalent Influenza Vaccine, hereafter referred to as Flu D-QIV (commercially available as Fluarix Quadrivalent in the US).
  - Sanofi's Fluzone High-Dose Quadrivalent Vaccine, hereafter referred to as Fluzone HD Quadrivalent (commercially available as Fluzone High-Dose Quadrivalent in the US).
  - GSK's Flu Dresden – Influenza Vaccine, hereafter referred to as Flu D-TIV (commercially available as Fluarix in the US).
  - Sanofi's Fluzone High-Dose Vaccine, hereafter referred to as Fluzone HD (commercially available as Fluzone High-Dose in the US).
- Strains included in study interventions (Flu mRNA formulations and comparators) will be based on World Health Organization (WHO) recommendation for influenza virus vaccine composition for Northern Hemisphere (NH) 2023-2024 for the initial part of the study, and NH 2024-2025 for protocol amendment 2. It should be noted that following the recent recommendations from WHO and Food and Drug Agency (FDA) Vaccines and Related Biological Products Advisory Committee (VRBPAC) to remove the B/Yamagata strain from influenza vaccine composition [WHO, 2023b; FDA, 2023], the Flu mRNA vaccine is now being developed as CCI [redacted]. The comparators will be licensed quadrivalent vaccines for the initial part of the study and licensed trivalent vaccines for protocol amendment 2, in line with the NH 2023-2024 and NH 2024-2025 recommendations, respectively.
- For the initial part of the study: 5 groups enrolled in parallel for YAs (4 Flu mRNA groups and 1 comparator group) and 5 groups enrolled in parallel for OAs (4 Flu mRNA groups and 1 comparator group). For protocol amendment 2: 2 groups enrolled in parallel for YAs (1 Flu mRNA group and 1 comparator group) and 2 groups enrolled in parallel for OAs (1 Flu mRNA group and 1 comparator group) (Table 5).

- Planned (approximate) number of participants to be enrolled: 250 YAs (50 participants per group) and 250 OAs (50 participants per group) in the initial part of the study, and 160 YAs (80 participants per group) and 160 OAs (80 participants per group) in protocol amendment 2.
- Method of study intervention allocation: a stratified permuted block randomization will be used in a 1:1 ratio allocation across groups. The stratification factors will include:
  - Country
  - Age group
  - Flu vaccination history in the preceding 2 years
- A subset representing approximately 50% of the total study population, randomly selected and equally distributed over the groups, will be defined for this study. This subset will be used to further characterize the humoral immune response, i.e., virus microneutralization (MN) titers CCI [redacted]. Refer to Section 6.3 for more details.
- Intended duration of the study per participant: approximately 6 months.
- Aspects of data collection: blood samples, safety events.
- Method of data collection:
  - Standardized electronic Case Report Form (eCRF).
  - Solicited events and the occurrence of unsolicited AEs will be collected using an electronic Diary (eDiary). Participants, with support from the site, will install the eDiary application on their own personal, handheld device (e.g., mobile phone, tablet) or the site will provide a device that is pre-programmed with the eDiary.
  - The collection of blood samples will be documented with a validated digital collection application for sample management.
- Safety monitoring: A blinded medical monitor, designated Safety Lead (or delegate) and SRT will continuously monitor available safety data throughout the study. If a potential safety concern/signal is identified that requires unblinded review, an unblinded internal Safety Review Committee (iSRC), independent from the project, will review available safety data. Refer to Section 8.3.6 for more information on safety monitoring strategy applicable to this study and to Section 10.1.6 for SRT and iSRC composition and role.
- Level of blinding: observer-blind. Refer to Section 6.4 for more information on blinding.
- Investigational study interventions CCI [redacted]. Refer to Section 6.1 for more details on the composition of study interventions to be administered.

Table 5 Study groups and interventions

Study groups	Study interventions	CCI [redacted]
Flu mRNA_1_YA	F2G22B/DL001Z[1]	
Flu mRNA_2_YA	F2H23D/DL001Z-NH[1]	
Flu mRNA_3_YA	F2H23B/DL001Z-NH[1]	
Flu mRNA_4_YA	F2H23H/DL001Z[1]	
Comparator_YA	FDQ23A-NH (Flu D-QIV) [1,4]	
Flu mRNA_9_YA*	GSK5800544A[2]	
Comparator_2_YA*	Flu D-TIV [2,4]	
Flu mRNA_5_OA	F2H23B/DL001Z-NH[1]	
Flu mRNA_6_OA	F2H23A/DL001Z-NH[1]	
Flu mRNA_7_OA	F2H23H/DL001Z[1]	
Flu mRNA_8_OA	F2H23G/DL001Z[1]	
Comparator_OA	Fluzone HD Quadrivalent[1,4]	
Flu mRNA_10_OA*	GSK5800544A[2]	
Comparator_2_OA*	Fluzone HD[2,4]	

HA: hemagglutinin; CCI [redacted]; B-Vic: B/Victoria lineage; YA: younger adult; OA: older adult.

* Applicable to protocol amendment 2.

[1] Strains used to design study interventions for the initial part of the study are based on WHO recommendation for influenza virus vaccine composition for the 2023-2024 NH season.

[2] Strains used to design study interventions for protocol amendment 2 are based on WHO recommendation for influenza virus vaccine composition for the 2024-2025 NH season.

[3] CCI [redacted] GSKVx000000048110; CCI [redacted] GSKVx000000040033; CCI [redacted] GSKVx000000034794; CCI [redacted]: GSKVx000000048111; CCI [redacted]: GSKVx000000034797; CCI [redacted] GSKVx000000034798. For protocol amendment 2: CCI [redacted] GSKVx000000048110; CCI [redacted]: GSKVx000000063073; CCI [redacted]: GSKVx000000034794; CCI [redacted]: GSKVx000000048111; CCI [redacted] GSKVx000000063074; CCI [redacted]: GSKVx000000034798

[4] Refer to Table 6 for the strains used in the comparator vaccines.

4.2. Scientific rationale for study design

The purpose of this Phase 2a study is to evaluate the immunogenicity and safety of the seasonal influenza investigational study interventions and, specifically, CCI [redacted]

Note that available clinical immunogenicity and reactogenicity data from this study and study FLU SV MRNA-002 have CCI [redacted] The objective of protocol amendment 2 is to consolidate the immunogenicity and reactogenicity data package for this formulation in both age groups CCI [redacted]

The study's primary objective and endpoints are based on the CCI [redacted]. The study is designed as an observer-blind study to ensure collection of unbiased safety data for the investigational study interventions to support the immunogenicity data findings.

The investigational study interventions will be compared to licensed seasonal influenza vaccines to enable a descriptive comparison of safety and immunogenicity to SoC. The comparators will be licensed quadrivalent vaccines for the initial part of the study and licensed trivalent vaccines for protocol amendment 2, in line with the NH 2023-2024 and NH 2024-2025 recommendations, respectively. The investigational study interventions will be CCI [redacted] to follow the recent recommendations from WHO and FDA VRBPAC to remove the B/Yamagata strain from influenza vaccine composition [WHO, 2023b; FDA, 2023].

The OA population is disproportionately affected by influenza complications and represents a high unmet need. In the study, the investigational study interventions will be evaluated in both YAs and OAs to confirm that any immunogenicity findings will be applicable for both age categories. The licensed seasonal influenza vaccines included as the comparator will be age-appropriate to optimize the SoC comparison.

As a considerable safety data package in both YAs and OAs (with no safety concerns observed at any dose levels evaluated) has been collected in the Phase 1 FLU SV MRNA-003 (217895) and Phase 1/2 FLU SV MRNA-002 (217884) studies, all study groups in both age categories will be enrolled in this study in parallel without restrictions.

4.3. Justification for dose

The purpose of this Phase 2a study is to explore possible ways CCI [redacted] in a CCI [redacted] HA CCI [redacted]. To achieve this, CCI [redacted]

Previous studies have evaluated CCI [redacted].

CCI [redacted]

4.4. End-of-study definition

A participant is considered to have completed the study if the participant has completed all periods of the study including the last visit or the last scheduled procedure shown in the SoA.

The EoS is defined as the date of the last subject last visit (Visit 3) or date of the last testing/reading of human biological samples related to primary and secondary endpoints, whichever occurs later. If EoS is not equal to LSLV, it must be achieved no later than 8 months after LSLV.

5. STUDY POPULATION

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

5.1. Inclusion criteria

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

- A male or female between and including 18 and 85 years of age (YAs: 18-64; OAs: 65-85) at the time of the study intervention administration. INC#1
- Healthy participants or medically stable patients as established by medical history and clinical examination. Participants with chronic medical conditions with or without specific treatment (e.g., chronic metabolic, cardiac, pulmonary, renal, hepatic, neurologic, and hematologic diseases) are allowed to participate in this study if considered by the investigator as medically stable. A stable medical condition is defined as disease not requiring significant change in therapy or hospitalization for worsening disease during 3 months before enrollment. INC#2
- Body mass index (BMI) $\geq$18 kg/m² and $\leq$35kg/m^2. INC#3
- Participants who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g., completion of the diary cards, return for follow-up visits), independently or with the assistance of a caregiver. INC#4

  Note: In case of physical incapacity that would preclude the self-completion of the eDiary, either site staff can assist the OA participant (for activities performed during site visits) or the participant may assign a caregiver to assist him/her with this activity (for activities performed at home or in the long-term care facility). However, at no time, the site staff or caregiver will evaluate the participant's health status while answering diaries and/or questionnaires or make decisions on behalf of the participant.
- Written informed consent obtained from the participant prior to performance of any study-specific procedure. INC#5

- Female participants of non-childbearing potential may be enrolled in the clinical study. Refer to Section 10.4.1 for definitions of WOCBP, menarche and menopause. INC#6
- Female participants of childbearing potential may be enrolled in the clinical study, if the participant:
  - Has practiced adequate contraception for 1 month prior to the study intervention administration, and
  - Has a negative pregnancy test within 24 hours prior to the study intervention administration, and
  - Has agreed to continue adequate contraception for at least 1 month after study intervention administration. INC#7

Refer to Section 10.4.1 for definitions of WOCBP and adequate contraception.

5.2. Exclusion criteria

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

5.2.1. Medical conditions

- Participant tested positive for influenza by local health authority-approved testing methods within 180 days prior to Day 1. EXC#1
- Current or past malignancy, unless completely resolved without sequelae for >5 years before the study intervention administration (excluding effectively treated basal cell skin cancer). EXC#2
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing required). HIV-infected individuals may be enrolled if they have been stable on antiretroviral therapy for the past 6 consecutive months, i.e., their treatment has not been modified, their CD4 cell count is ≥200/mm^3 and their viral load has been undetectable (i.e., HIV-RNA <50 copies/mL) (based on medical records, no laboratory testing required). EXC#3
- Participants with a history of, or current suspicion of myocarditis, pericarditis, or idiopathic cardiomyopathy (including a history of myocarditis or pericarditis following vaccination with an mRNA COVID-19 vaccine), or presence of any medical condition that increases risk of myocarditis or pericarditis, including cocaine abuse, cardiomyopathy, endomyocardial fibrosis, hypereosinophilic syndrome, hypersensitivity myocarditis, eosinophilic granulomatosis with polyangiitis and persistent myocardial infection will be excluded from the study EXC#4
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the study intervention (including polyethylene glycol, egg proteins and aminoglycoside antibiotics). EXC#5
- Hypersensitivity to latex. EXC#6

- Recurrent history or uncontrolled neurological disorders or seizures, including Guillain-Barré syndrome and Bell's palsy, with the exception of febrile seizures during childhood. EXC#7
- Any history of dementia or any medical condition that moderately or severely impairs cognition. EXC#8
- Any condition that in the judgment of the investigator would make intramuscular injection unsafe. EXC#9
- Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the participant due to participation in the clinical study. EXC#10

5.2.2. Prior/Concomitant therapy

- Administration of an influenza vaccine within 180 days before enrollment or planned administration prior to Visit 2 (Day 29) after the study intervention administration. EXC#11
- Previous vaccination with a mRNA influenza vaccine. EXC#12
- Administration of a vaccine not foreseen by the study protocol in the period starting 30 days (Day -30) before the study intervention administration, or planned administration within 28 days (Visit 2 [Day 29]) after the study intervention administration*. EXC#13

  **If emergency mass vaccination for an unforeseen public health threat (e.g., a pandemic) is recommended and/or organized by public health authorities outside the routine immunization program, the time period described above can be reduced, provided it is used according to the local governmental recommendations and sponsor is notified*.
- Use of any investigational or non-registered product (drug, vaccine or invasive medical device) other than the study intervention during the period beginning 30 days before the study intervention administration, or their planned use during the study period. EXC#14
- Administration of immunoglobulins and/or any blood products or plasma derivatives during the period starting 90 days before the study intervention administration or planned administration during the study period. EXC#15
- Chronic administration of immune-modifying drugs (defined as more than 14 consecutive days in total) and/or planned use of long-acting immune-modifying treatments at any time up to the end of the study.
  - Up to 3 months prior to the study intervention administration:

  For corticosteroids, this will mean prednisone equivalent ≥20 mg/day. Inhaled, intraarticular and topical steroids are allowed.

  - Up to 3 months prior to study intervention administration: long-acting immune-modifying drugs including among others immunotherapy (e.g., TNF-inhibitors), monoclonal antibodies, antitumoral medication. EXC#16

5.2.3. Prior/Concurrent clinical study experience

- Concurrently participating in another clinical study, at any time during the study period, in which the participant has been or will be exposed to an investigational or a non-investigational intervention (drug/invasive medical device). EXC#17

5.2.4. Other exclusion criteria

- Pregnant or lactating female participant. EXC#18
- Bedridden participants. EXC#19
- Female participant planning to become pregnant or planning to discontinue contraceptive precautions within the 1-month post-dosing period. EXC#20
- History of chronic alcohol consumption and/or drug abuse in the past 5 years as deemed by the investigator to render the potential participant unable/unlikely to provide accurate safety reports or comply with study procedures. EXC#21
- Any study personnel or their immediate dependents, family, or household members. EXC#22
- Participants with extensive tattoos covering deltoid region on both arms that would preclude the assessment of local reactogenicity. EXC#23

5.3. Lifestyle considerations

No lifestyle restrictions are required for this study.

5.4. Screen failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently assigned/randomized to study intervention/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes, but not limited to informed consent date, demography, screen failure details and eligibility criteria.

5.5. Criteria for temporarily delaying administration of study intervention

Study intervention administration may be postponed until transient conditions cited below are resolved:

- Acute disease and/or fever at the time of randomization and/or study intervention administration. Fever is defined as a temperature ≥ 38.0°C/100.4°F by any route. The route for measuring temperature can be oral, axillary or tympanic. The preferred location for measuring temperature will be the oral cavity.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

The definition of study intervention is provided in the DEFINITIONS OF TERMS.

6.1. Study intervention(s) administered

Investigational study interventions listed in Table 6 CCI [redacted]
CCI [redacted]
CCI [redacted]

Table 6 Study intervention(s) administered (table spreading through multiple pages)

Study intervention name	Flu Seasonal mRNA					
	F2H23D/DL001Z-NH		F2H23B/DL001Z-NH		F2H23A/DL001Z-NH	
Study intervention formulation	CCI [redacted]					
Presentation	Concentrate for dispersion for injection (vial)	solution for dispersion for injection (vial or ampoule)	Concentrate for dispersion for injection (vial)	solution for dispersion for injection (vial or ampoule)	Concentrate for dispersion for injection (vial)	solution for dispersion for injection (vial or ampoule)
Type	Biologic		Biologic		Biologic	
Use	Investigational		Investigational		Investigational	
Route of administration	IM		IM		IM	
Administration site						
• Location	Deltoid		Deltoid		Deltoid	
• Directionality	Upper		Upper		Upper	
• Laterality[1]	Non-dominant		Non-dominant		Non-dominant	
Number of doses to be administered	1		1		1	

Volume to be administered by dose[2]	0.5 mL		0.5 mL		0.5 mL	
Sourcing	Provided centrally by the sponsor		Provided centrally by the sponsor		Provided centrally by the sponsor	
Packaging and labeling	Refer to the pharmacy manual for more details		Refer to the pharmacy manual for more details		Refer to the pharmacy manual for more details	
Manufacturer	GSK Biologicals	Pfizer	GSK Biologicals	Pfizer	GSK Biologicals	Pfizer

Study intervention name	**Flu Seasonal mRNA**					
	F2G22B/DL001Z		**F2H23G/DL001Z**		**F2H23H/DL001Z**	
Study intervention formulation	CCI [redacted]					
Presentation	Concentrate for dispersion for injection (vial)	solution for dispersion for injection (vial or ampoule)	Concentrate for dispersion for injection (vial)	solution for dispersion for injection (vial or ampoule)	Concentrate for dispersion for injection (vial)	solution for dispersion for injection (vial or ampoule)
Type	Biologic		Biologic		Biologic	
Use	Investigational		Investigational		Investigational	

Study intervention name	**Flu Seasonal mRNA**					
	F2G22B/DL001Z		**F2H23G/DL001Z**		**F2H23H/DL001Z**	
Route of administration	IM		IM		IM	
Administration site						
• **Location**	Deltoid		Deltoid		Deltoid	
• **Directionality**	Upper		Upper		Upper	
• **Laterality**[1]	Non-dominant		Non-dominant		Non-dominant	
Number of doses to be administered	1		1		1	
Volume to be administered by dose[2]	0.5 mL		0.5 mL		0.5 mL	
Sourcing	Provided centrally by the sponsor		Provided centrally by the sponsor		Provided centrally by the sponsor	
Packaging and labeling	Refer to the pharmacy manual for more details		Refer to the pharmacy manual for more details		Refer to the pharmacy manual for more details	
Manufacturer	GSK Biologicals	Pfizer	GSK Biologicals	Pfizer	GSK Biologicals	Pfizer

Study intervention name	**FDQ23A-NH (Flu D-QIV)**	**Fluzone HD Quadrivalent**
Study intervention formulation	A/Victoria/4897/2022 (H1N1), IVR-238 (15 µg HA); A/Darwin/06/2021 (H3N2), IVR-227 (15 µg HA); B/Austria/1359417/2021, BVR-26 (15 µg HA); B/Phuket/3073/2013 (15 µg HA); Water for injections	A/Victoria/4897/2022 (H1N1), IVR-238 (60 µg HA); A/Darwin/09/2021 (H3N2), SAN-010 (60 µg HA); B/Michigan/01/2021 (60 µg HA); B/Phuket/3073/2013 (60 µg HA); Sodium phosphate-buffered isotonic sodium chloride solution
Presentation	Suspension for injection (syringe)	Suspension for injection (syringe)
Type	Combination product	Combination product
Use	Comparator	Comparator
Route of administration	IM	IM

Study intervention name	FDQ23A-NH (Flu D-QIV)	Fluzone HD Quadrivalent
Administration site		
• **Location**	Deltoid	Deltoid
• **Directionality**	Upper	Upper
• **Laterality**[1]	Non-dominant	Non-dominant
Number of doses to be administered	1	1
Volume to be administered by dose[2]	0.5 mL	0.7 mL
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and labeling	Refer to the pharmacy manual for more details	Refer to the pharmacy manual for more details
Manufacturer	GSK Biologicals	Sanofi Pasteur

Study intervention name	Flu Seasonal mRNA (protocol amendment 2)		Comparators (protocol amendment 2)	
	GSK5800544A		Flu D-TIV	Fluzone HD
Study intervention formulation	CCI [redacted]		A/Victoria/4897/2022 (H1N1), IVR-238 (15 µg HA); A/Thailand/8/2022 (H3N2), IVR-237 (15 µg HA); B/Austria/1359417/2021, BVR-26 (15 µg HA); Water for injections	A/Victoria/4897/2022 (H1N1), IVR-238 (60 µg HA); A/California/122/2022 (H3N2), SAN-022 (60 µg HA); B/Michigan/01/2021 (Victoria lineage) (60 µg HA); Sodium phosphate-buffered isotonic sodium chloride solution
Presentation	Concentrate for dispersion for injection (vial)	solution for dispersion for injection (vial or ampoule)	Suspension for injection (syringe)	Suspension for injection (syringe)
Type	Biologic		Combination product	Combination product
Use	Investigational		Comparator	Comparator

Study intervention name	**Flu Seasonal mRNA (protocol amendment 2)**		**Comparators (protocol amendment 2)**	
	GSK5800544A		**Flu D-TIV**	**Fluzone HD**
Route of administration	IM		IM	IM
Administration site				
• **Location**	Deltoid		Deltoid	Deltoid
• **Directionality**	Upper		Upper	Upper
• **Laterality**[1]	Non-dominant		Non-dominant	Non-dominant
Number of doses to be administered	1		1	1
Volume to be administered by dose[2]	0.5 mL		0.5 mL	0.5 mL
Sourcing	Provided centrally by the sponsor		Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and labeling	Refer to the pharmacy manual for more details		Refer to the pharmacy manual for more details	Refer to the pharmacy manual for more details
Manufacturer	GSK Biologicals	Pfizer	GSK Biologicals	Sanofi Pasteur

HA: hemagglutinin; IM: intramuscular; NH: Northern hemisphere; WHO: World Health Organization

[1] The non-dominant arm is the preferred arm of injection. In case it is not possible to administer the study intervention in the non-dominant arm, an injection in the dominant arm may be performed.

[2] Refer to the pharmacy manual for the volume after re-constitution

Study participants must be observed closely for at least 30 minutes after the administration of the study intervention. Appropriate medical treatment must be readily available during the observation period in case of anaphylaxis, syncope.

6.1.1. Medical devices

- Licensed vaccines used as comparator in this study are provided as a single-dose pre-filled syringe (i.e., considered as combination product).
- Other medical devices (not manufactured by or for sponsor, e.g., syringes, thermometers) may be provided for use in this study.
- Instructions for medical device use are provided in the study Pharmacy Manual.
- All device deficiencies (including malfunction, use error and inadequate labeling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.4.9 and Section 10.5) and appropriately managed by GSK.

6.2. Preparation, handling, storage, and accountability

- Instructions for the preparation of study interventions are provided in Pharmacy Manual.
- The investigator or designee must confirm appropriate conditions (e.g., temperature) have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply, prepare, or administer study intervention.
- All study intervention must be stored in a secure, environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3. Assignment to study intervention

The randomization order of study intervention assignment is created by a GSK Randomization Generation system. A stratified and permuted block approach is employed to maintain equal study intervention balance within each stratum. In addition, a subset representing approximately 50% of the total study population, will be randomly selected and equally represented by study intervention within stratum CCI [redacted] CCI [redacted].

All participants will be centrally randomized to study intervention using a GSK Randomization and Trial Supply Management (RTSM) system. Study intervention will be assigned randomization number (study intervention number) and dispensed at Visit 1.

For additional information about the study intervention number allocation or when RTSM system is not available, please refer to the Pharmacy Manual.

6.4. Blinding

This study will be observer-blind. Refer to DEFINITIONS OF TERMS for definition of observer-blind.

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

A participant may continue in the study if that participant's intervention assignment is unblinded.

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

6.4.1. Emergency unblinding

RTSM will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator may, at the investigator's discretion, contact GSK to discuss the situation prior to unblinding a participant's intervention assignment unless this could delay emergency treatment for the participant. If a participant's intervention assignment is unblinded, GSK must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded.

If the investigator is unable to access RTSM, they can contact the GSK helpdesk based on the information provided in the Pharmacy Manual.

A physician other than the investigator (e.g., an emergency room physician) or participant/participant's caregiver or family member may also request emergency access to the participant's study intervention information as per participant card.

6.5. Study intervention compliance

When participants are dosed at the site, they will receive study intervention directly from the authorized site staff, under medical supervision. The date and time of each dose administered in the clinic and the treatment number will be recorded in the source documents.

6.6. Dose modification

Not applicable.

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

Not applicable.

6.8. Treatment of overdose

Not applicable.

6.9. Prior and concomitant therapy

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

The following prior and concomitant medication(s)/product(s)/vaccine(s) must be recorded in the eCRF:

- All concomitant medications, including vaccines/products, administered after the study intervention administration (Day 1) until Visit 2 (Day 29).
- Administration of any influenza vaccine 2 years prior to dosing and up to Visit 3 (Day 183).
- All concomitant medications leading to withdrawal including vaccines/products, administered after the study intervention administration (Day 1) until Visit 3 (Day 183). Refer to Section 5.2.2 for more information.
- All concomitant medications, which may explain/cause/be used to treat a MAAE including vaccines/products administered after the study intervention administration (Day 1) until Visit 3 (Day 183).
- All concomitant medications, which may explain/cause/be used to treat an SAE/AESI including vaccines/products from Day 1 until Visit 3 (Day 183), as defined in Section 8.4.1 and Section 10.3.5. These must also be recorded in the Expedited Adverse Event report.

- Prophylactic medication (i.e., medication administered in the absence of any symptom and in anticipation of a reaction to the vaccination) including any antipyretics and/or analgesics from Day 1 to Day 7.
- Vitamins and dietary supplements should not be recorded in the eCRF.

Any medication or vaccine (including over-the-counter or prescription medicines) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of study intervention

Not applicable.

7.2. Participant discontinuation/withdrawal from the clinical study

A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).

A participant may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.

The participant will be permanently discontinued from the study intervention and the study at that time.

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

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

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

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

- AE
- Death
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Site terminated by Sponsor
- Study terminated by Sponsor
- Withdrawal by participant
- Other (specify).

Participants who are withdrawn from the study because of AEs/SAEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigator will follow participants who are withdrawn from the study due to an AE/SAE until the event is resolved (see Section 10.3.5.5).

7.3. Lost to follow-up

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. Participants who have signed informed consent but are not eligible to proceed should be recorded in the eCRF with a status of "screen failure."
- In the event of a significant study-continuity issue (e.g., caused by a pandemic), alternate strategies for participant visits, assessments, study intervention distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements.

Study participants may decide to assign a caregiver to help them complete the study procedures. Please refer to the DEFINITIONS OF TERMS for the definition of a caregiver.

A caregiver can be appointed by the participant at any time during the study, when the participant feels it is necessary. Caregiver should receive the caregiver information letter before providing support to the study participant. Ideally, a single caregiver should be appointed by the participant but, in some situations, it may happen that several caregivers will support a study participant throughout the conduct of the study. This should be recorded in the source documents. However, every effort should be done to ensure that only 1 caregiver enters the data into eDiary to allow for timely completion.

Caregivers may help the study participants with performing some practical study procedures such as receiving or making phone calls to site staff, planning study visits, entering participant's responses into eDiary, transportation to and from the study site etc. However, at no time, the caregiver should evaluate the participant's health status while answering diaries or make decisions on behalf of the participant. At the first study visit (Visit 1 [Day 1]) the site staff should inform the participant of the possibility to appoint a caregiver. Then at subsequent study visit(s), the site staff should check again with the participants if they wish to appoint a caregiver or if there were or will be changes of caregiver.

8.1. Administrative and baseline procedures

8.1.1. Collection of demographic data

Record demographic data such as year of birth, sex, race, and ethnicity in the participant's eCRF.

Collection of sex, race and ethnicity data is necessary to assess and monitor the diversity of the trial participants, and to determine if the trial participants are truly representative of the impacted population.

8.1.2. Medical/vaccination history

Obtain the participant's medical/vaccination history by interviewing the participant and/or review of the participant's medical records. Record any pre-existing conditions, signs and/or symptoms present prior to the study intervention administration in the eCRF. Flu vaccination history for the past 2 years must also be recorded in the eCRF.

8.1.3. Provision of eDiary device or installing of eDiary application on participant's personal device

Participants will be encouraged to bring their own personal electronic devices (e.g., smart phone or tablet) to Visit 1 (Day 1). The study staff will check the compatibility of the participant's device with respect to the eDiary application.

At Visit 1 (Day 1), with support from the study staff, the participant will install the eDiary application on their own electronic device. Participants who do not wish to use their own device for study purposes or whose device is incompatible with the eDiary application, will be provided an electronic device by the study staff. The provisioned devices will have the study eDiary application already installed.

The eDiary application will be used by the participant to self-report information related to their health post-dosing (e.g., solicited events). The study staff will train the participant and/or their caregiver (if identified by the study participant) on the use of the eDiary and emphasize the importance of completing the eDiary on a daily basis throughout the eDiary data collection period.

Refer to Section 8.4.1 for details of collection of safety information and Section 10.3.5 for guidelines.

8.2. Immunogenicity assessments

Planned timepoints for all immunogenicity assessments are provided in the SoA.

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

Findings in this or future studies may make it desirable to use samples acquired in this study, initially not planned in this protocol, for further research and/or further characterizing the disease or condition studied and/or the immune response of the vaccine. To this end, all participants in countries where this is allowed will also be asked, at the time of giving consent to join this study, to give consent to allow GSK or a contracted partner, to use the samples for further research. The further research will be subject to prior IEC/IRB approval, if required by local legislation.

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

8.2.1. Biological samples

An overall blood volume of approximately 45 mL* will be collected from each participant during the entire study period. Refer to Table 7 and SoA for information on volumes collected for different assessments. Refer to Laboratory Manual for details on collection, processing, storage and shipment of biospecimens.

** Given that samples at Day 183 will only be collected from participants who did not receive a SoC vaccination against seasonal flu after Visit 2 and prior to Day 183, this volume represents the maximum volume that will be collected over the study period for participants who will have a sample collected at Day 183.*

Table 7 Biological samples

Sample type	Quantity	Unit	Timepoint
Blood	~15	mL	Visit 1 (Day 1)
Blood	~15	mL	Visit 2 (Day 2)
Blood	~15	mL	Visit 3 (Day 183)[1]

1 Blood samples should only be collected for participants who did not receive a SoC vaccination against seasonal flu after Visit 2 and prior to this visit.

8.2.2. Laboratory assays

Table 8 Laboratory assays

Test classification	System	Component	Method	Laboratory
Humoral Immunity	Serum	CCI [redacted] CCI		GSK or GSK designated lab

[1] In case of technical assay development issue, testing for this strain might not be done.

Clinical testing with assays supporting tertiary endpoints where analyses might be deemed futile due to the other study results might not be performed.

Additional testing on collected samples might be done to gain a better understanding of the vaccine(s), of the clinical study data and/or of the disease. These additional assays may not be represented in the objectives/endpoints of the study protocol.

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

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

8.2.3. Immunological read-outs

Table 9 Immunological read-outs

Blood sampling timepoint		Group/ Subset name[1]	No. participants (approximate)	Component
Type of contact and timepoint	Sampling timepoint			
Visit 1 (Day 1)	Pre-dose	All participants	820	CCI [redacted]
		Subset	410	
Visit 2 (Day 29)	Post-dose	All participants	820	
		Subset	410	
Visit 3 (Day 183)	Post-dose	All participants	820[2]	
		Subset	410[2]	

No = Number.
[1]Refer to Section 4.1 for the description of subset
[2] Given that samples at Visit 3 will only be collected from participants who did not receive a SoC vaccination against seasonal flu after Visit 2 and prior to this visit, this number represents the maximum number of participants who will have a sample collected for the Visit 3.

8.2.4. Immunological correlates of protection (CoP)

CCI [redacted]

8.3. Safety assessments

Planned timepoints for all safety assessments are provided in the SoA.

8.3.1. Physical examination

- Prior to the study intervention administration at Visit 1 (Day 1), the investigator will perform physical examination of the participant including assessment of resting vital signs: systolic/diastolic blood pressure, heart rate and respiratory rate after at least 5 minutes of rest, body weight and height. Vital signs are to be taken before blood collection for laboratory tests.
- If the participant reported any pre-existing medical condition, the investigator would extend the physical examination according to their medical judgment to ensure that the participant meets all the inclusion/exclusion criteria.
- If the investigator determines that the participant's health on the day of study intervention administration temporarily precludes dosing, the visit will be

rescheduled. See Section 5.5 for the list of criteria for temporary delay of study intervention administration. Treatment of any abnormality observed during this examination has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

- Physical examination at each study visit after the study intervention administration visit (Visit 1 [Day 1]) will be performed only if the participant indicates during questioning that there might be some underlying pathology(ies) or if deemed necessary by the investigator or delegate.
- In case of suspected myocarditis or pericarditis and an unscheduled site visit, the investigator will perform physical examination of the participant including assessment of resting vital signs: systolic/diastolic blood pressure, heart rate and respiratory rate after at least 5 minutes of rest, body weight and height, and blood oxygen saturation.

8.3.2. Pre-dosing body temperature

The body temperature of each participant needs to be measured prior to the study intervention administration and recorded in the eCRF. If the participant has fever on the day of dosing, the study intervention administration visit will be rescheduled. Refer to the SoA (Section 1.3) for the definition of fever for this study and preferred location for body temperature measurement.

8.3.3. Warnings and precautions to administration of study intervention

Warnings and precautions to administration of study intervention must be checked at Visit 1 (Day 1) prior to study intervention administration, as specified in SoA. For comparators, refer to the approved product label/package insert.

8.3.4. Myocarditis and pericarditis assessment and definitions

All participants will be educated on the symptoms that might indicate myocarditis or pericarditis and will receive guidance on contacting study personnel and seeking medical care if any of these symptoms occur. All potential cases of myocarditis or pericarditis should undergo diagnostic work and be clinically evaluated as recommended by international guidelines (e.g., guidance from the American Heart Association and American College of Cardiology).

Following vaccination, participants reporting at least 1 of the following symptoms must contact the study site immediately and must be clinically evaluated:

- acute chest pain, pressure, or discomfort
- dyspnea, shortness of breath or pain with breathing
- palpitations
- syncope.

For these participants, if myocarditis or pericarditis is suspected according to the clinical judgment of the investigator, an unscheduled site visit should take place**,** except in case of medical emergency in which case the participant should be directed to seek immediate medical care as required.

Based on symptomatology and physical examination, the investigator should arrange an electrocardiogram (ECG) and a blood sample for measurement of troponin (troponin I and/or troponin T). If no facilities are available on site, referral for ECG and/or troponin can be made elsewhere (for example, an emergency room). Referral should be expedited if necessary, according to the clinical judgment of the investigator.

If the ECG and/or troponin testing and/or physical examination show abnormalities (see pre-specified abnormalities, Section 10.2), the participant should be referred to a cardiologist for further evaluation and management following current practice guidelines (e.g., American Heart Association or local standard of care). Where possible, other investigations should include echocardiography and/or cardiac MRI.

For study participants presenting with cardiac symptoms and pre-specified ECG abnormalities, and/or abnormal troponin level and/or abnormal physical examination consistent with myocarditis or pericarditis, the AE myocarditis/pericarditis should be recorded as an AESI and reported to the sponsor within 24 hours. For these study participants, the eCRF should be completed with full details of cardiac signs and symptoms, physical examination, ECG, and troponin results, as well as results of any other investigations carried out (including echocardiography and cardiac MRI, if applicable, see Section 10.2 for details). The findings of the investigations should be reported to the sponsor within 24 hours of being available.

Participants who have myocarditis or pericarditis will be followed until resolution of symptoms and/or cardiac evaluation has been completed, whichever comes last.

8.3.5. Pregnancy testing

- A urine pregnancy test must be performed for all female participants of childbearing potential before the administration of the study intervention. Pregnancy testing must be done even if the participant is menstruating at the time of the study visit. The study intervention may only be administered if the pregnancy test is negative.
- See Section 8.4.6 for the information on study continuation for participants who become pregnant during the study.

8.3.6. Safety monitoring, committees, and pausing criteria

- Participant safety will be continuously monitored by the investigator, the medical monitor, the designated Safety Lead (or delegate) and the SRT throughout the study. Pertinent findings and conclusions are shared with the product's SRT for review of the overall benefit-risk profile of the product.
- The investigator, medical monitor, designated Safety Lead (or delegate) and SRT are blinded to participant treatment assignment. If a potential safety concern/signal is

identified that requires unblinded review, an unblinded internal Safety Review Committee (iSRC), independent from the project/product, will review available safety data.

- The nature and duration of safety monitoring activities are specified in the SoA (Section 1.3) and in the endpoints (Section 3).

Refer to Section 10.1.6 for the SRT and iSRC composition and role.

8.3.6.1. Study pausing criteria

The investigator and the SRT will monitor safety in a blinded manner, including but not limited to the pausing criteria outlined in Table 10. Pausing criteria mean criteria leading to a pause in vaccination, to enable expedited review of all information by iSRC and Sponsor to assess if a temporary halt of the study is warranted or not.

To enable prompt response to a situation that could trigger a pause of vaccinations, the investigator must notify the Sponsor via the appropriate reporting system or the Sponsor's medical monitor or designee, whichever applies, immediately and no later than 24 hours after becoming aware of any fatalities, SAEs, Grade 3 solicited or unsolicited AEs (within the specified period of follow-up for unsolicited events and considered related to vaccination by the investigator), and update the eCRF with relevant information on the same day the AE information is collected.

If a pausing criterion is potentially met based on blinded assessment by the investigator and/or SRT, the unblinded iSRC (chair) will confirm as soon as possible and no later than within 24 hours from notification whether the pausing criterion is met by assessing if the event(s) occurred in the (same) investigational group and impacted participants have not received licensed control. Only for pausing criterion 1a (see Table 10 below), the investigator must conservatively suspend further dosing at his/her site while this assessment occurs.

Once a pausing criterion is confirmed to be met, the Sponsor will inform the investigator(s), triggering a pause in further dosing in all sites and at all dose levels in all study groups until iSRC has reviewed the relevant data. iSRC has the right to decide which data is unblinded for their review.

A pause in further dosing can also be recommended by iSRC at any time during the study to investigate any potential (safety) concern, regardless of whether any pausing criteria were met.

Once a pause is in place, the Sponsor will expeditiously further evaluate the relevant data, and based on iSRC recommendation, will take the decision whether the pause can be lifted or whether other steps such as a temporary halt, or modification or stopping of the study are required.

Communications regarding any temporary halt and/or decisions regarding study continuation to investigators, relevant Ethics Committees, IRBs and applicable Health Authorities will be done as appropriate and in compliance with local regulations.

Table 10 Study pausing criteria

Pausing criteria	Event	Number of participants per dose & individual investigational study group (i.e., non-licensed vaccines)
1a	Death or any life-threatening SAE for which there is no alternative attributable cause as per Investigator assessment	≥1[1]
1b	Any non-life-threatening SAE that is considered related to vaccination as per Investigator or Sponsor assessment	≥1[1]
1c	Necrosis at the injection site	≥1[1]
1d	Confirmed myocarditis or pericarditis events not clearly attributable to any cause other than study vaccine	≥1[1]
1e	Anaphylaxis, unless clearly attributable to a cause other than study vaccine	≥1[1]
2a	Similar (Preferred Terms in same HLT based on MedDRA coding) Grade 3 unsolicited AEs, considered related to vaccination as per Investigator assessment, with an event onset within the specified period of follow-up for unsolicited events	≥2[2]

AE=Adverse event; HLT = High level term; iSRC = Internal safety review committee; MedDRA = Medical dictionary for regulatory activities; SAE = Serious adverse event.

[1] After the first iSRC meeting triggered by the occurrence of this pausing criterion, each additional participant meeting this pausing criterion will thereafter trigger a pause and iSRC review.

[2] After the first iSRC meeting triggered by the occurrence of a given pausing criterion for a given event, the iSRC will indicate the conditions under which it requires further notification and review of the subsequent same/similar events.

8.4. Adverse events, serious adverse events, and other safety reporting

For definitions relating to safety information see Section 10.3.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and other safety information and remain responsible for following up all AEs (see Section 8.4.3). This includes events reported by the participant (or, when appropriate, by a caregiver).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3 and Section 10.5.

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

All SAEs, AESIs, MAAEs, and AEs leading to withdrawal will be collected from the day of study intervention administration (Day 1) until Visit 3 (Day 183) at the time points specified in the SoA.

SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) will be collected from the time a participant consents to participate in the study.

All AEs will be collected from the start of study intervention until Day 7 (for solicited events) or Day 28 (for unsolicited AEs) at the timepoints specified in the SoA.

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

Complete list of safety events to be collected in this study and the timeframes for their collection and reporting are provided in Table 11.

Table 11 Collection and reporting of safety information

Event	Pre-Dose[1]	Dose D1	D7	D28	D183
Administration site solicited events		■			
Systemic solicited events		■			
Unsolicited AEs		■	■		
SAEs		■	■	■	
SAEs related to study participation, study intervention, or to a concurrent GSK medication/vaccine	■	■	■	■	
AESIs		■	■	■	
Pregnancies		■	■	■	
AEs leading to withdrawal from study		■	■	■	
Intercurrent medical conditions		■	■	■	
MAAEs		■	■	■	

AE: adverse event; AESI: adverse event of special interest; MAAE: medically attended adverse event; SAE: serious adverse event.

[1] i.e., consent obtained.

The details on the follow-up of AE and SAE can be accessed in Section 8.4.3. The shaded regions in the table indicate time period of data collection.

All SAEs will be recorded and reported to the sponsor immediately and under no circumstance should this exceed 24 hours, as indicated in Section 8.4.5, Section 10.3 and Section 10.5. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

For the timeframes for reporting AESIs see Section 8.4.5, Table 13.

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 11.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, after a participant has been discharged from the study, the investigator must record it in the medical records per the local country requirements. If the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

See Section 8.4.7 for contact information.

8.4.2. Method of detecting AEs and SAEs

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

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AESIs (as defined in Section 8.4.4) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.5.5 and Section 10.5.4.4.

The investigator should follow-up on influenza-like illness (ILI) cases occurring during the study and aim to confirm the diagnosis by local health authority-approved testing methods for flu detection. These cases will be considered as intercurrent medical conditions and will be managed as described in Section 8.4.1 and Section 9.2.

8.4.4. AESIs

8.4.4.1. Potential immune-mediated diseases (pIMDs)

pIMDs are a subset of AESIs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune etiology. AEs that need to be recorded and reported as pIMDs include those listed in the Table 12.

In order to facilitate the documentation of pIMDs in the eCRF, a pIMD standard questionnaire, and a list of preferred terms (PTs) and PT codes corresponding to the below diagnoses will be available to investigators at study start.

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

Table 12 List of pIMDs

Blood disorders and coagulopathies	**Cardio-pulmonary inflammatory disorders**	**Endocrine disorders**

• Antiphospholipid syndrome
• Autoimmune aplastic anemia
• Autoimmune hemolytic anemia, including:
  • Warm antibody hemolytic anemia
  • Cold antibody hemolytic anemia
• Autoimmune lymphoproliferative syndrome (ALPS)
• Autoimmune neutropenia
• Autoimmune pancytopenia
• Autoimmune thrombocytopenia
  • Frequently used related terms include: “autoimmune thrombocytopenic purpura”, “idiopathic thrombocytopenic purpura (ITP)”, “idiopathic immune thrombocytopenia”, “primary immune thrombocytopenia”.
• Evans syndrome
• Pernicious anemia
• Thrombosis with thrombocytopenia syndrome (TTS)
• Thrombotic thrombocytopenic purpura
  • Also known as “Moschcowitz-syndrome” or “microangiopathic hemolytic anemia”
	• Idiopathic pulmonary fibrosis, including:
	  • Idiopathic interstitial pneumonia (Interstitial lung disease, Pulmonary fibrosis, Immune-mediated pneumonitis)
	  • Pleuroparenchymal fibroelastosis (PPFE)
	• Pulmonary alveolar proteinosis (PAP)
	  • Frequently used related terms include: “pulmonary alveolar lipoproteinosis”, “phospholipidosis”
		• Addison’s disease
		• Autoimmune / Immune-mediated thyroiditis, including:
		  • Hashimoto thyroiditis (autoimmune hypothyroidism, lymphocytic thyroiditis)
		  • Atrophic thyroiditis
		  • Silent thyroiditis
		  • Thyrotoxicosis
		• Autoimmune diseases of the testis and ovary, including:
		  • Autoimmune oophoritis
		  • Autoimmune ovarian failure
		  • Autoimmune orchitis
		• Autoimmune hyperlipidemia
		• Autoimmune hypophysitis
		• Diabetes mellitus type I
		• Graves’ or Basedow’s disease, including:
		  • Marine Lenhart syndrome
		  • Graves' ophthalmopathy, also known as thyroid eye disease (TED) or endocrine ophthalmopathy
		• Insulin autoimmune syndrome
		• Polyglandular autoimmune syndrome, including:
		  • Polyglandular autoimmune syndrome type I, II and III

Eye disorders	**Gastrointestinal disorders**	**Hepatobiliary disorders**

• Ocular Autoimmune / Immune-mediated disorders, including:
  • Acute macular neuroretinopathy (also known
	• Autoimmune / Immune-mediated pancreatitis
	• Celiac disease
	• Inflammatory Bowel disease, including:
	  • Crohn’s disease
		• Autoimmune cholangitis
		• Autoimmune hepatitis
		• Primary biliary cirrhosis
		• Primary sclerosing cholangitis

as acute macular outer retinopathy) • Autoimmune/Immune-mediated retinopathy • Autoimmune/Immune-mediated uveitis, including idiopathic uveitis and sympathetic ophthalmia • Cogan's syndrome: an oculo-audiovestibular disease • Ocular pemphigoid • Ulcerative keratitis • Vogt-Koyanagi-Harada disease	• Microscopic colitis • Terminal ileitis • Ulcerative colitis • Ulcerative proctitis	
Musculoskeletal and connective tissue disorders	**Neuroinflammatory/neuromuscular disorders**	**Renal disorders**

• Gout, including:
  • Gouty arthritis
• Idiopathic inflammatory myopathies, including:
  • Dermatomyositis
  • Inclusion body myositis
  • Immune-mediated necrotizing myopathy
  • Polymyositis
• Mixed connective tissue disorder
• Polymyalgia rheumatica (PMR)
• Psoriatic arthritis (PsA)
• Relapsing polychondritis
• Rheumatoid arthritis, including:
  • Rheumatoid arthritis associated conditions
  • Juvenile idiopathic arthritis
  • Palindromic rheumatism
  • Still's disease
  • Felty's syndrome
• Sjogren's syndrome
• Spondyloarthritis, including:
  • Ankylosing spondylitis
  • Juvenile spondyloarthritis
  • Keratoderma blenorrhagica
  • Psoriatic spondylitis
  • Reactive Arthritis
  • Undifferentiated spondyloarthritis
• Systemic Lupus Erythematosus, including:
  • Lupus associated conditions (e.g., Cutaneous lupus erythematosus, Lupus nephritis, etc.)
  • Complications such as shrinking lung syndrome (SLS)
	• Acute disseminated encephalomyelitis (ADEM) and other inflammatory-demyelinating variants, including:
	  • Acute necrotising myelitis
	  • Bickerstaff's brainstem encephalitis
	  • Disseminated necrotizing leukoencephalopathy (also known as Weston-Hurst syndrome, acute hemorrhagic leuko-encephalitis, or acute necrotizing hemorrhagic encephalomyelitis)
	  • Myelin oligodendrocyte glycoprotein antibody-associated disease
	  • Neuromyelitis optica (also known as Devic's disease)
	  • Noninfective encephalitis/ encephalomyelitis / myelitis
	  • Postimmunization encephalomyelitis
	• Guillain-Barré syndrome (GBS)*, including:
	  • Variants such as Miller Fisher syndrome and the acute motor and sensory axonal neuropathy (AMSAN)
	• Idiopathic cranial nerve palsies/paresis and inflammations (neuritis), including:
	  • Cranial nerve neuritis (e.g., Optic neuritis)
		• Autoimmune/Immune-mediated glomerulonephritis, including:
		  • IgA nephropathy
		  • IgM nephropathy
		  • C1q nephropathy
		  • Fibrillary glomerulonephritis
		  • Glomerulonephritis rapidly progressive
		  • Membranoproliferative glomerulonephritis
		  • Membranous glomerulonephritis
		  • Mesangioproliferative glomerulonephritis
		  • Tubulointerstitial nephritis and uveitis syndrome

• Systemic Scleroderma (Systemic Sclerosis), including:
  • Raynaud's syndrome
  • Systemic sclerosis with diffuse scleroderma
  • Systemic sclerosis with limited scleroderma (also known as CREST syndrome)
	• Idiopathic nerve palsies/paresis (e.g., Bell's palsy)
	  • Melkersson-Rosenthal syndrome
	  • Multiple cranial nerve palsies/paresis
	• Multiple Sclerosis (MS), including:
	  • Clinically isolated syndrome (CIS)
	  • Malignant MS (the Marburg type of MS)
	  • Primary-progressive MS (PPMS)
	  • Radiologically isolated syndrome (RIS)
	  • Relapsing-remitting MS (RRMS)
	  • Secondary-progressive MS (SPMS)
	  • Uhthoff's phenomenon
	• Myasthenia gravis, including:
	  • Ocular myasthenia
	  • Lambert-Eaton myasthenic syndrome
	• Narcolepsy (with or without presence of unambiguous cataplexy)
	• Peripheral inflammatory demyelinating neuropathies and plexopathies, including
	  • Acute Brachial Radiculitis (also known as Parsonage-Turner Syndrome or neuralgic amyotrophy)
	  • Antibody-mediated demyelinating neuropathy
	  • Chronic idiopathic axonal polyneuropathy (CIAP)
	  • Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP), including atypical CIDP variants (e.g., multifocal acquired demyelinating sensory and motor neuropathy also known as Lewis-Sumner syndrome)
	  • Multifocal motor neuropathy (MMN)
	• Transverse myelitis (TM), including:
	  • Acute partial transverse myelitis (APTM)	

	• Acute complete transverse myelitis (ACTM)	
Skin and subcutaneous tissue disorders	**Vasculitis**	**Other (including multisystemic)**

• Alopecia areata
• Autoimmune / Immune-mediated blistering dermatoses, including:
  • Bullous Dermatitis
  • Bullous Pemphigoid
  • Dermatitis herpetiformis
  • Epidermolysis bullosa acquisita (EBA)
  • Linear IgA-mediated bullous dermatosis (LABD), also known as Linear IgA disease
  • Pemphigus
• Erythema multiforme
• Erythema nodosum
• Lichen planus, including:
  • Liquen planopilaris
• Localised Scleroderma (Morphoea)
  • Eosinophilic fasciitis (also called Shulman syndrome)
• Psoriasis
• Pyoderma gangrenosum
• Reactive granulomatous dermatitis, including:
  • Interstitial granulomatous dermatitis
  • Palisaded neutrophilic granulomatous dermatitis
• Stevens-Johnson Syndrome (SJS), including:
  • Toxic Epidermal Necrolysis (TEN)
  • SJS-TEN overlap
• Sweet's syndrome, including:
  • Acute febrile neutrophilic dermatosis
• Vitiligo
	• Large vessels vasculitis*, including:
	  • Arteritic anterior ischemic optic neuropathy (AAION or arteritic AION)
	  • Giant cell arteritis (also called temporal arteritis)
	  • Takayasu's arteritis
	• Medium sized and/or small vessels vasculitis*, including:
	  • Anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified)
	  • Behcet's syndrome
	  • Buerger's disease (thromboangiitis obliterans)
	  • Churg–Strauss syndrome (allergic granulomatous angiitis)
	  • Erythema induratum (also known as nodular vasculitis)
	  • Henoch-Schonlein purpura (also known as IgA vasculitis)
	  • Microscopic polyangiitis
	  • Necrotizing vasculitis
	  • Polyarteritis nodosa
	  • Single organ cutaneous vasculitis, including leukocytoclastic vasculitis, hypersensitivity vasculitis and acute hemorrhagic edema of infancy (AHEI)
	  • Granulomatosis with polyangiitis
		• Anti-synthetase syndrome
		• Capillary leak syndrome
		  • Frequently used related terms include: "systemic capillary leak syndrome (SCLS)" or "Clarkson's Syndrome"
		• Goodpasture syndrome
		  • Frequently used related terms include: "pulmonary renal syndrome" and "anti-Glomerular Basement Membrane disease (anti-GBM disease)"
		• Immune-mediated enhancement of disease, including:
		  • Vaccine associated enhanced disease (VAED and VAERD). Frequently used related terms include "vaccine-mediated enhanced disease (VMED)", "enhanced respiratory disease (ERD)", "vaccine-induced enhancement of infection", "disease enhancement", "immune enhancement", and "antibody-dependent enhancement
		• Immunoglobulin G4 related disease
		• Langerhans' cell histiocytosis
		• Multisystem inflammatory syndromes, including:
		  • Kawasaki's disease
		  • Multisystem inflammatory syndrome in adults (MIS-A)
		  • Multisystem inflammatory syndrome in children (MIS-C)
		• Overlap syndrome
		• Raynaud's phenomenon
		• Sarcoidosis, including:
		  • Loefgren syndrome
		• Susac's syndrome

Note: Table 12 contains diseases/conditions which do not necessarily match MedDRA PTs, given the frequent MedDRA updates

8.4.4.2. Other AESIs

The following events are also considered as AESIs in this study.

- Severe hypersensitivity reactions within 24 hours after study intervention administration
- Myocarditis/pericarditis. Refer to Section 8.3.4 for myocarditis/pericarditis assessment and definitions.

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

8.4.5. Regulatory reporting requirements for SAEs/AESIs

- Prompt notification by the investigator to the sponsor of an SAE/AESI is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met. See Section 8.4.1 for reporting timeframes.
- For SAEs/AESIs, the investigator must always provide an assessment of causality at the time of the initial report, as defined in the Section 10.3.5.3.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigators have to report to the sponsor pregnancies, medication errors, abuse and misuse even in an absence of an AE/SAE as these may be subjected to local regulatory reporting requirements for the sponsor.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

Table 13 Timeframes for submitting SAEs, AESIs and pregnancies to GSK

Type of event	Initial reports		Follow-up of relevant information on a previous report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours[1,2]	paper/electronic AEs report	24 hours[2]	paper/electronic AEs report
Pregnancies	24 hours[2]	paper pregnancy notification report/electronic pregnancy report	24 hours[2]	paper pregnancy follow-up report/electronic pregnancy report
AESIs	24 hours[1,3]	paper/electronic AEs report	24 hours[2]	paper/electronic AEs report

AE = adverse event; AESIs = adverse event of special interest; SAE = serious adverse event.

[1] Paper AEs Report will be dated and signed by the investigator (or designee). For each SAE/AESI, the investigator(s) must document in the medical notes that they have reviewed the SAE/AESI and have provided an assessment of causality.

[2] Timeframe allowed after receipt or awareness of the information by the investigator/site staff.

[3] Timeframe allowed once the investigator determines that the event meets the protocol definition of an AESI.

8.4.6. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention (Visit 1 [Day 1]) and until Visit 3 (Day 183).
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female participant pregnancy.
- Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The female participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the female participant and the neonate and the information will be forwarded to the sponsor. See Table 13 for reporting timeframes.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will be allowed to continue the study until the end unless she withdraws consent or the investigator decides that it is in the participant's best interest to be discontinued from the study.

8.4.7. Contact information for reporting SAEs, AESIs, pregnancies and study pausing criteria

Table 14 Contact information for reporting SAEs, AESIs, pregnancies and study pausing criteria

Study contact for questions regarding SAEs, AESIs, pregnancies and SAEs linked to device deficiencies Contact GSK's local and/or medical contacts	**Study contact for reporting of study pausing criteria** If a pausing criterion is met, the investigator must immediately inform the GSK's local and/or medical contacts
Contacts for reporting SAEs, AESIs, pregnancies and SAEs linked to device deficiencies Available 24/24 hours and 7/7 days ogm28723@gsk.com Fax: +32 2 656 8009	**Backup study contact for escalation of study pausing criteria** Refer to the local study contact information document.

AESI = adverse event of special interest; GSK = GlaxoSmithKline Biologicals SA; SAE = serious adverse event

8.4.8. Participant card

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

8.4.9. Medical device deficiencies

Medical devices are being provided for use in this study as the study intervention. To fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

If the site(s) uses non-sponsor medical devices, i.e., medical devices not provided by GSK, then the investigators are obligated to report any device deficiencies to the legal manufacturer of the devices directly.

The definition of a medical device deficiency can be found in Section 10.5.

Note: Deficiencies fulfilling the definition of an AE/SAE will follow the processes outlined in Section 10.5 of the protocol.

8.4.9.1. Time period for detecting medical device deficiencies

- Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such a deficiency is considered reasonably

related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting medical device deficiencies is provided in Section 10.5.

8.4.9.2. Follow-up of medical device deficiencies

- Follow-up applies to all participants, including those who discontinue study intervention.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

8.4.9.3. Prompt reporting of device deficiencies to the sponsor

- Device deficiencies will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a medical device deficiency.
- The medical device deficiency report form will be sent to the sponsor by email. If email is unavailable, then fax should be utilized.
- The sponsor will be the contact for the receipt of device deficiency reports.

8.4.9.4. Regulatory reporting requirements for device deficiencies

- The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.

8.5. Pharmacokinetics

Pharmacokinetics is not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamics is not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity assessments

Immunogenicity is described in Section 8.2.

8.10. Health economics

Health economics are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

The SAP will be finalized prior to first participant first visit and it will include a more technical and detailed description of the statistical analyses including demography, tertiary endpoint analyses and supporting analyses, if applicable. This Section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1. Statistical hypotheses

There is no formal hypothesis testing in this study; where statistical methods are applied, the emphasis will be on estimation with 95% confidence intervals (CIs).

9.2. Analysis sets

Table 15 Analysis sets

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	All participants who were screened for eligibility.	Study Population
Enrolled	Participants who received the study intervention, had an immunogenicity blood draw at pre-dose or were randomized. Note that as per good clinical practice (GCP) enrolled participants should have completed the informed consent process and participants should be eligible before initiating any study procedure. Note: screening failures (who never passed screening, even if rescreened) and participants screened but never enrolled into the study (met eligibility but not needed) are excluded from the Enrolled analysis set as they did not enter the study.	Study Population
Exposed	All participants who received the study intervention. Analysis per group is based on the study intervention administered.	Safety
Per Protocol Set (PPS)	All eligible participants who received a study intervention dose as per protocol, had immunogenicity results at both Day 1 and Day 29 for at least 1 vaccine [redacted] antigen, complied with Day 1 and Day 29 blood draw intervals (refer to Table 2), without intercurrent conditions* that may interfere with immunogenicity and without prohibited concomitant medication/vaccination before Visit 2 (Day 29). Immunogenicity data at Day 183 will be censored in case of non-compliance with the blood sample visit, in case intercurrent conditions* that may interfere with immunogenicity have occurred, or if prohibited concomitant medication/vaccination were taken before Day 183. The analysis will be done according to the study intervention that participants received.	Demography, Immunogenicity

* Note: Intercurrent medical conditions that may lead to elimination of immunogenicity results from the PPS are the occurrence of either a confirmed immunodeficiency condition, new malignancy, or development of confirmed influenza disease.

9.3. Statistical analyses

The primary and secondary endpoints are described in Section 3. The primary analyses of immunogenicity endpoints will be based on the PPS. The analysis of reactogenicity and safety endpoints will be based on the Exposed Set (ES). All analyses at interim will be based on ES.

All analyses will be done separately for OAs and YAs, unless specified otherwise.

Missing data will not be imputed unless otherwise indicated.

9.3.1. Definitions

Abbreviation/term	Definition
CCI SCR	The percentage of dosed participants who have either a CCI pre-dose titer <1:10 and a post-dosing CCI titer CCI or a pre-dose CCI titer CCI and at least a CCI increase in post-dosing CCI titer.
CCI SCR	CCI
CCI	The percentage of dosed participants with a CCI ≥1:40.

CCI SCR: seroconversion rate; CCI .

9.3.2. Primary and secondary endpoints analyses

9.3.2.1. Analysis of immunogenicity endpoints

The group differences between each investigational study intervention candidate and the comparator group will be assessed separately as follows for each CCI antigen:

- At each post-dosing timepoint and for each age group separately, the 2-sided CI for between-group GMT ratio between investigational study intervention and (over) the comparator group will be derived from an ANCOVA model on $\log_{10}$ transformed concentration. The ANCOVA model will include group (i.e., each of the investigational study intervention and the comparator group), actual age of participants, country, flu vaccination history in the preceding 2 years, and $\log_{10}$-transformed titer at pre-dosing as fixed effects. The adjusted GMT and GMI in each group will be obtained from the same model with 95% CI. Missing data will not be replaced.
- For a given age group, the 2-sided 95% CI for the group difference in SCR between an investigational study intervention and (minus) the comparator group will be computed at Day 29 based on the method of Miettinen and Nurminen [Miettinen, 1985].
- For CCI only: the percentage of participants achieving CCI , defined as having post-dosing titer CCI will be summarized by age group with associated exact 95% CI.

Titer values below the assay CCI will be replaced by CCI .

All analyses will be performed separately for each age group and study part (where part 1 consists of the study groups in the initial part of the study and part 2 consists of the study groups in the protocol amendment 2), unless otherwise indicated.

9.3.2.2. Analysis of reactogenicity and safety endpoints

The percentage of participants reporting each individual solicited administration site event (any grade, Grade ≥2, Grade 3 and MAAEs) and solicited systemic event (any grade, Grade ≥2, Grade ≥3 and MAAEs) within the 7-day follow-up period (i.e., Day 1-Day 7 post-dosing) will be tabulated for each group according to the maximum grade in Day 1-Day 7 period.

The same summaries will be generated for any administration site solicited events, any systemic solicited events, and any solicited events.

When available, information related to solicited events (e.g., occurrence, grading) collected by study staff when daily eDiary is missing/incorrect will be used in these summaries.

The verbatim reports of unsolicited AEs will be reviewed by a qualified person and the signs and symptoms will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) Dictionary for Adverse Reaction Terminology. Every verbatim term will be matched with the appropriate PT. The percentage of participants with any unsolicited AEs within the 28-day follow-up period (i.e., Day 1 to Day 28 post-dosing) with its exact 95% CI will be tabulated by group and by MedDRA PT and System Organ Class (SOC). Similar tabulation will be done for Grade 3 unsolicited AEs, for any causally related unsolicited AEs, for Grade 3 causally related unsolicited AEs and for unsolicited AEs resulting in a medically attended visit.

The percentage of participants with at least 1 report of SAE, with at least 1 report of MAAE and with at least 1 report of AESI, respectively, classified by the MedDRA SOC and PT and reported from Day 1 up to study end will be tabulated with exact 95% CI.

The percentage of participants using concomitant medication (any medication, any antipyretic and any antipyretic taken prophylactically, respectively) during the 28-day follow-up period (i.e., Day 1 to Day 28 post-dosing) will be summarized by group.

9.4. Interim analyses

9.4.1. Sequence of interim analyses and other planned analyses

In addition to the analyses detailed below, additional analyses (e.g., safety analyses) may be conducted to support the SRT and iSRC decisions, as described in Section 8.3.6. Refer to the Section 10.1.6 for the SRT and iSRC roles.

A primary completion analysis (PCA) is foreseen and will be conducted upon availability of all primary and secondary endpoints up to Day 29 for participants enrolled in parallel in the 4 Flu mRNA groups and 1 comparator group per age category of the initial part of the study CCI [redacted]

An interim analysis will be conducted upon availability of all primary and secondary endpoints up to Day 29 for participants enrolled in parallel in 1 Flu mRNA group and 1

comparator group per age category of protocol amendment 2 to enable consolidation of the immunogenicity and reactogenicity data package for the selected dose formulation CCI [redacted] An additional interim analysis will be performed based on availability of safety endpoints up to last visit (Day 183) for participants enrolled in the initial part of the study.

A restricted study team will be unblinded to individual participant data and all efforts will be made to ensure the participants, investigators and monitoring staff blinding is maintained up to study end. The rest of the study team will have access to aggregated unblinded summaries but will remain blinded to individual participant data and treatment assignment until the end of the study. It is possible, however, due to the limited sample size, that unblinding occurs for a few participants having a specific AE or SAE (e.g., an AE/SAE occurring only in a single participant). Therefore, anyone having access to the results could become unblinded regarding those few specific cases.

Note that the Day 29 interim analysis will be triggered once the planned number of subjects have had up to Day 29 safety follow-up and immunogenicity blood draw collected. Considering potential over-enrolments, all other participants not included in this analysis, will be included in the final analysis.

A final analysis with all primary and secondary endpoints obtained until the last visit (Day 183) will be performed and made available to the investigators and submitted to regulatory authorities, as appropriate.

Analysis of tertiary endpoints may be performed at a later stage.

9.5. Sample size determination

The primary objective is to explore how the different candidates of Flu mRNA vaccine compare to licensed comparator group(s).

In the initial part of the study, the sample size of 47 evaluable participants in each dose level cohort and age group, is expected to provide a 95% CI for group difference in SCR with a lower half-width ≤ 20% for difference in SCR for the different strains (Table 16) and a 95% CI with an expected half-width of 1.6 fold for the group GMT ratio considering a population standard deviation of 0.5 in $\log_{10}$ transformed GMT post-dosing and 5% of unevaluable participants per group.

Table 16 Half-width of 95% CI for the group difference in seroconversion rates by comparator and CCI (Evaluable N per group = 47)

Comparator	CCI	Proportion (%)[1]	95% CI of Proportion (%)[1]	Lower Half-width of 95 CI (%)
Flu D-QIV		59.3	57.5; 61.1	20
Flu D-QIV		76.2	72.3; 79.6	18
Flu D-QIV		68.3	63.6; 72.8	19
Fluzone HD Quadrivalent		43.3	39.4; 47.3	19
Fluzone HD Quadrivalent		51.0	48.3; 52.9	20
Fluzone HD Quadrivalent		62.0	50.1; 71.8	20

CCI

CCI

CCI

Flu D-QIV: GSK's Flu Dresden-Quadrivalent Influenza Vaccine; Fluzone HD Quadrivalent: *Sanofi's Fluzone High-Dose Quadrivalent Vaccine*.

In part 2 of the study (protocol amendment 2), a sample size of 76 evaluable participants in each study group and age group, is expected to provide a 95% CI for group difference in SCR with a lower half-width ≤ 16% for difference in SCR for the different strains (Table 17) and a 95% CI with an expected half-width of 1.45 fold for the group GMT ratio considering a population standard deviation of 0.5 in $\log_{10}$ transformed GMT post-dosing and 5% of unevaluable participants per group. The increased sample size is aimed at increasing the level of precision for the estimated CIs.

Table 17 Half-width of 95% CI for the group difference in seroconversion rates by comparator and CCI in part 2 of the study (protocol amendment 2) (Evaluable N per group = 76)

Comparator	CCI	Proportion (%)[1]	95% CI of Proportion (%)[1]	Lower Half-width of 95 CI (%)
Flu D-TIV		59.3	57.5; 61.1	16
Flu D-TIV		76.2	72.3; 79.6	14
Flu D-TIV		68.3	63.6; 72.8	15
Fluzone HD		43.3	39.4; 47.3	15
Fluzone HD		51.0	48.3; 52.9	16
Fluzone HD		62.0	50.1; 71.8	16

CCI

CCI

CCI

Flu D-TIV: GSK's Flu Dresden Influenza Vaccine; Fluzone HD: *Sanofi's Fluzone High-Dose Vaccine*.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1. Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines.
  - Applicable ICH GCP guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, and all other applicable local regulations.

10.1.2. Financial disclosure

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

10.1.3. Informed consent process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participants and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. They will be required to physically sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection (e.g., HIPAA and GDPR requirements), where applicable, and the IRB/IEC or study center.
- Sample testing will be done in accordance with the recorded consent of the individual participant.
- By default, collected samples for the study will be stored for a maximum of 20 years. This storage period begins when the last participant completes the last study visit. This timeline can be adapted based on local laws, regulations or guidelines requiring different timeframes or procedures. In all cases, the storage period should be aligned with participant's consent. These additional requirements must be formally communicated to, discussed and agreed with GSK.
- The medical record must include a statement that physical informed consent was obtained before the participant was enrolled in the study and the date the physical consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A physical copy of the ICF(s) must be provided to the participant.

The ICF will contain a separate section that addresses the use of remaining samples for optional further research related and not related to this study. The investigator or authorized designee will explain to each participant the objectives of the further research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

In case of unexpected pregnancy, participant must be informed that personal information (PI) such as date of birth, sex of the baby will be collected as part of safety follow-up. Consent for collection of information about the baby may be obtained from the participant and/or their partner as per local regulations.

10.1.4. Recruitment strategy

Printed and digitalized advertising and recruitment materials may be used to support recruitment.

All advertisement and participant's facing materials will be approved as per local regulations before their use.

10.1.5. Data protection

- Participants will be assigned a unique identifier by the investigator. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- Validated digital collection application will be used by sites to track collection of laboratory samples. Participant's identification number and individual QR code will be used to identify blood samples at the time of sample collection/processing. However, no personal information or lab data will be captured in this application.
- GSK will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study.
- The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant, that their data will be used as described in the informed consent.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between sponsor and study sites specifies responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.
- GSK has a global, internal policy that requires all GSK staff and complementary workers to report data incidents or breaches immediately, using dedicated tools. Clear procedures are defined for assessing and investigating data breaches to identify and to take appropriate remediation steps, to contain and to mitigate any risks for individuals resulting from a breach, in compliance with applicable laws.

10.1.6. Committees structure

- A SRT is in place for each GSK product. It comprises a global cross-functional team responsible for the ongoing assessment of benefit-risk for a product. The SRT contribute to the continual assessment of incoming new efficacy and safety information. The SRT includes safety, clinical, and statistics experts from GSK . The role of the SRT is to oversee the safety of participants and study conduct (in blinded fashion).

- The iSRC is a cross-functional committee including safety, clinical, and statistics experts from GSK. The iSRC members are independent of the project. The role of the iSRC is to oversee the safety of participants and study conduct if unblinded review is required.

For more details, refer to the SRT framework and the iSRC charter.

10.1.7. Dissemination of clinical study data

- The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Study Register in compliance with applicable regulations/GSK policy. GSK will aim to register protocols summaries prior to study start and target results summaries submission within 12 months of primary/ study completion date (adult population). Where external regulations require earlier disclosure, GSK will follow those timelines.
- Where required by regulation, summaries will also be posted on applicable national or regional clinical study registers.
- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and provided reasonable access to statistical tables, figures, and relevant reports. GSK will also provide the investigator with the full summary of the study results, including a summary of trial results understandable to laypersons. The investigator is encouraged to share the layperson summary of results with the study participants, as appropriate. The full study report will be made available upon request, after decision on marketing authorization by regulatory authorities.
- Where required by regulation, the names of the sponsor signatory and investigator signatory will be made public.
- GSK will provide the investigator with the randomization codes and participant-level line listings for their site only after completion of the full statistical analysis.
- GSK intends to make anonymized participant-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding. Data will be shared with researchers in a non-identifying way, and appropriate measures will be taken to protect PI; these measures will comply with data protection and privacy laws that apply.

10.1.8. Data quality assurance

- All participant data relating to the study will be recorded on printed or eCRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- Guidance on completion of eCRFs will be provided in eCRF completion guidelines.

- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- Quality Tolerance Limits (QTLs) will be predefined in the QTL Report to identify systematic issues that can impact participant right, safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the Clinical Study Report (CSR).
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring, involvement of central reading mechanism) methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on site monitoring) are provided in the monitoring plan.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for a minimum period of 15 years from the issue of the final CSR/equivalent summary, or in accordance with applicable law, whichever is longer. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. In the event of a conflict between this protocol and the fully executed clinical study agreement, the protocol shall prevail with respect to records retention.

10.1.9. Source documents

- For this study there will be no source data recorded directly into the eCRF (i.e., no prior written or electronic record of data is available).
- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the eCRF/eDiaries or entered in the eCRF/eDiaries that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- For this study there will be source data recorded directly into the validated digital collection application for samples management (i.e., sample identifier). Data reported in the digital collection application or entered in it that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.

- Definition of what constitutes source data and its origin can be found in DEFINITIONS OF TERMS.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The sponsor or designee will perform monitoring to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.10. Study and site start and closure

Start of study and first act of recruitment

The start of study and the first act of recruitment are defined as FSFV (first ICF signature date) at a country-level.

Study/Site termination

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

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

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

For study termination:

- Discontinuation of further study intervention development.

For site termination:

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

If the study is prematurely terminated or temporarily suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or temporary suspension, as specified by the applicable regulatory requirements. The

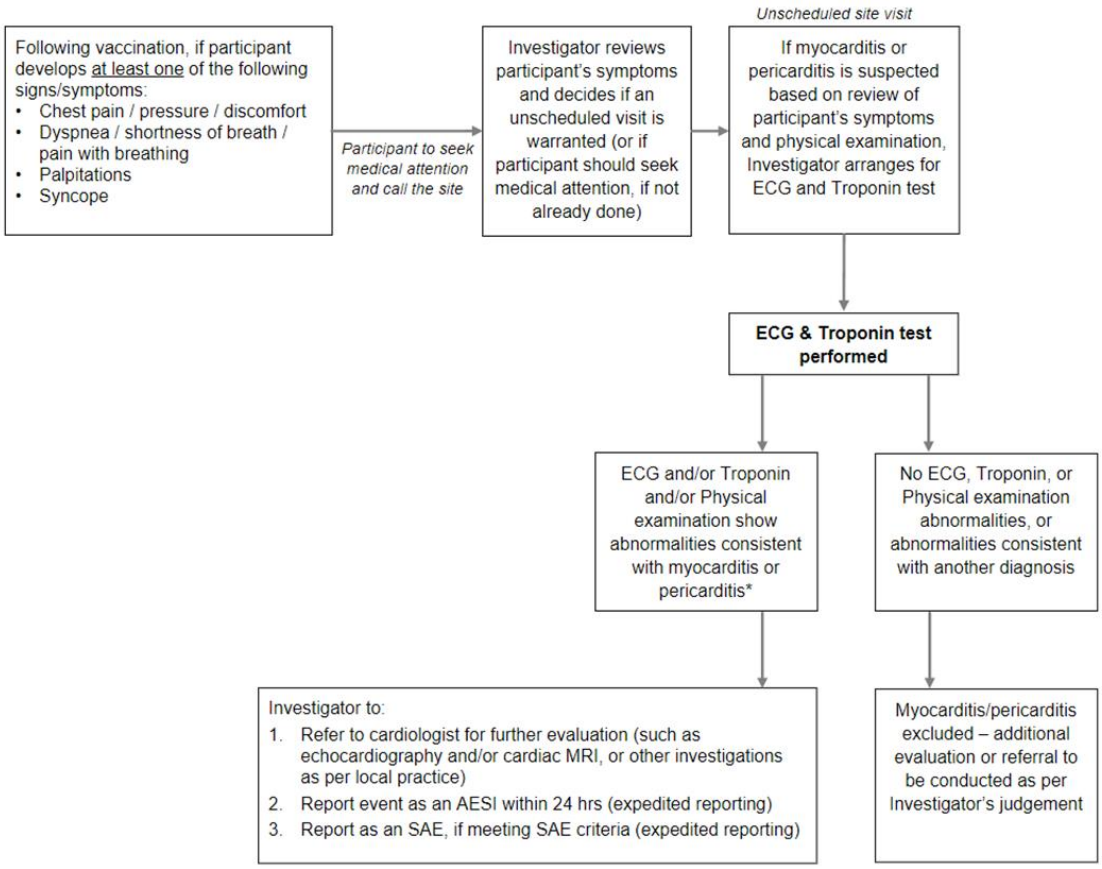
investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.11. Publication policy

GSK seeks to publish medically or scientifically significant results in searchable peer-reviewed scientific literature within 18 months from LSLV. We follow International Committee of Medical Journal Editors standards for authorship and use Good Publications practices to guide our publications.

10.2. Appendix 2: Myocarditis and pericarditis

10.2.1. Myocarditis and pericarditis workflow



*Abnormalities triggering cardiology referral
** AESIs will be referred for independent evaluation and diagnosis of myocarditis and pericarditis

Abnormalities triggering cardiology referral include:

1. Electrocardiogram abnormalities:
    - ST-segment or T-wave abnormalities;
    - Paroxysmal or sustained atrial, supraventricular, or ventricular arrhythmias; or

- AV nodal conduction delays or intraventricular conduction defects.
- PR-depression

2. Troponin level above upper limit of normal (any type of troponin)
3. Pericardial rub on physical examination

10.2.2. Case definitions of probable and confirmed myocarditis, pericarditis, and myopericarditis

Condition	Definition	
Acute myocarditis	**Probable case**	**Confirmed case**
	Presence of **≥1 new** or worsening of the following clinical symptoms:1 • Chest pain, pressure, or discomfort • Dyspnea, shortness of breath, or pain with breathing • Palpitations • Syncope	Presence of **≥1 new** or worsening of the following clinical symptoms:1 • Chest pain, pressure, or discomfort • Dyspnea, shortness of breath, or pain with breathing • Palpitations • Syncope
	AND	**AND**
	≥1 new finding of: • Troponin level above upper limit of normal (any type of troponin) • Abnormal ECG or rhythm monitoring findings consistent with myocarditis[3] • Abnormal cardiac function or wall motion abnormalities on echocardiogram • Cardiac MRI findings consistent with myocarditis[4]	**≥1 new** finding of: • Histopathologic confirmation of myocarditis[2] • Cardiac MRI findings consistent with myocarditis[4] in the presence of troponin level above upper limit of normal (any type of troponin)
	AND	**AND**
	No other identifiable cause of the symptoms and findings	No other identifiable cause of the symptoms and findings
Acute pericarditis[5]	Presence of **≥2 new** or worsening of the following clinical features: • Acute chest pain6 • Pericardial rub on exam • New ST-elevation or PR-depression on ECG • New or worsening pericardial effusion on echocardiogram or MRI	
Myopericarditis	This term may be used for patients who meet criteria for both myocarditis and pericarditis.	

MRI: magnetic resonance imaging; ECG: electrocardiogram

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

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

[3] To meet the ECG or rhythm monitoring criterion, a probable case must include at least one of 1) ST-segment or T-wave abnormalities; 2) Paroxysmal or sustained atrial, supraventricular, or ventricular arrhythmias; or 3) AV nodal conduction delays or intraventricular conduction defects.

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

[5] Refer to Adler et al. [Adler, 2015].

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

10.3. Appendix 3: AEs and SAEs: Definitions and procedures for recording, evaluating, follow-up, and reporting

10.3.1. Definition of AE

AE definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. • Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

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

Events NOT meeting the AE definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital, admission for routine examination.). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. Pre-existing diseases will be recorded in the medical history section of the eCRF. • Hospitalization for elective treatment of a pre-existing condition (known or diagnosed before signing the informed consent) that did not worsen from baseline.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
a. Results in death.
b. Is life-threatening. The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization. • In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity. • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea,

	influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e.	Is a congenital anomaly/birth defect in the offspring of a study participant.
f.	Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy).
g.	Is a suspected transmission of any infectious agent via an authorized medicinal product.
h.	Other situations: • Possible Hy's Law case: ALT ≥3x ULN AND total bilirubin ≥2x ULN (for participants with known Gilbert's syndrome these criteria only apply if total bilirubin ≥2xULN, and direct bilirubin ≥2xULN and at least doubled from baseline value) or INR >1.5 must be reported as SAE. • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Solicited events

• **Definition of solicited event**
• Solicited events are predefined administration site events and systemic events for which the participant is specifically questioned, and which are noted by the participant in their eDiary.

a. Solicited administration site events

The following administration site events will be solicited:

Table 18 Solicited administration site events

All age groups
Pain at administration site
Redness at administration site
Swelling at administration site
Lymphadenopathy[1]

[1] Defined as localized axillary, cervical or supraclavicular swelling or tenderness ipsilateral to the injection arm.

b. Solicited systemic events

The following systemic events will be solicited:

Table 19 Solicited systemic events

Fever
Headache
Myalgia (muscle pain)
Arthralgia (joint pain)
Fatigue (tiredness)
Chills

Note: Participants will be instructed to measure and record the temperature in the evening. If additional temperature measurements are taken at other times of the day, participants will be instructed to record the highest temperature in the eDiary. The preferred location for measuring temperature will be the oral cavity.

10.3.4. Unsolicited AE

- **Definition of unsolicited AE**

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

10.3.5. Recording, assessment, and follow-up of AEs, SAEs, AESIs, and pregnancies

10.3.5.1. AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the paper Expedited Adverse Events Report/eCRF.

- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant identifier, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

An eDiary will be used in this study to capture solicited administration site or systemic events and the occurrence of unsolicited AEs. The participant should be trained on how and when to complete the eDiary.

Anyone who measures administration site or systemic events and who will record the event in the eDiary should be trained on using the eDiary. This training must be documented in the participant's source record.

For each solicited and unsolicited AE the participant experiences, the participant will be asked if they received medical attention (defined as unscheduled visit to or from medical personnel for any reason, including emergency room visits). This information will be recorded in the participant's eDiary and in the participant's eCRF as part of normal AE reporting (for unsolicited AEs). If the collection of solicited events was not possible for any reasons via the eDiary and solicited events were reported to the investigator by the participant, then it would be possible for it to be reported directly to the site staff and submitted (e.g., via the eCRF). Medical attention received for SAEs/AESIs will have to be reported using the normal AE reporting process in the eCRF.

If any individual other than the participant is making entries in the eDiary, their identity must be documented in the participant's source record.

All solicited events that occur during 7 days following administration of the dose of study intervention (Day 1 to Day 7) must be recorded into the eDiary, irrespective of intensity. An automatic reminder to complete the eDiary will be sent to the participants during this time frame. The solicited events ongoing at Day 7 will be followed up until resolution using eDiary.

The occurrence of all unsolicited AE during 28 days following the administration of the dose study intervention (Day 1 to Day 28) must be recorded into the eDiary. An automatic reminder to complete the eDiary will be sent to the participants during this time frame.

eDiary device should be returned to the site after the end of the relevant data collection period on Day 29 (Visit 2)*. If eDiary application was installed on participant's own device, it must be uninstalled after Day 29*.

**The return of the eDiary might be postponed if the solicited event is ongoing beyond Day 28.*

Daily eDiary compliance will be checked by the investigator or delegate on the eDiary portal. In case of non-compliance, the investigator should contact the participant to

remind the importance of daily entries. All other AEs occurring within this time frame should be recorded into the appropriate section of the eCRF, irrespective of their intensity or whether or not they are considered related to the study intervention.

After review and verbal discussion of the eDiary entries with the participant, if there are eDiary errors, the investigator will complete his/her own assessment in the relevant sections of the eCRF.

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

10.3.5.2. Assessment of intensity

The investigator will make an assessment of intensity for each AE, AESI, SAE, and device deficiency reported during the study and assign it to one of the following categories:

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

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

Table 20 Intensity scales for solicited events in participants of 6 years of age or more

Event	Intensity grade	Parameter
Pain at administration site	0	None.
	1	Mild: Any pain neither interfering with nor preventing normal everyday activities.
	2	Moderate: Painful when limb is moved and interferes with everyday activities.
	3	Severe: Significant pain at rest. Prevents normal everyday activities.
Redness at administration site[1]	0	<25 mm
	1	≥25 - ≤50 mm
	2	≥51 - ≤100 mm
	3	>100 mm
Swelling at administration site[1]	0	<25 mm
	1	≥25 - ≤50 mm

Event	Intensity grade	Parameter
	2	≥51 - ≤100 mm
	3	>100 mm
Lymphadenopathy[2]	0	None
	1	Mild: lymphadenopathy present but does not interfere with activity
	2	Moderate: lymphadenopathy that interferes with normal activity
	3	Severe: lymphadenopathy that prevents normal activity
Fever[3]	0	<38.0°C (100.4°F)
	1	≥38.0°C (100.4°F) - ≤38.4°C (101.1°F)
	2	≥38.5°C (101.2°F) - ≤38.9°C (102.0°F)
	3	≥39°C (102.1°F)
Headache	0	None
	1	Mild: Symptom is present but does not interfere with activity.
	2	Moderate: Interferes with normal activity.
	3	Severe: Prevents normal activity.
Myalgia (muscle pain)	0	None
	1	Mild: Symptom is present but does not interfere with activity.
	2	Moderate: Interferes with normal activity.
	3	Severe: Prevents normal activity.
Arthralgia (joint pain)	0	None.
	1	Mild: Symptom is present but does not interfere with activity.
	2	Moderate: Interferes with normal activity.
	3	Severe: prevents normal activity.
Fatigue	0	None
	1	Mild: Symptom is present but does not interfere with activity.
	2	Moderate: Interferes with normal activity.
	3	Severe: Prevents normal activity.
Chills	0	None
	1	Mild: chills present but do not interfere with activity
	2	Moderate: chills that interfere with normal activity
	3	Severe: chills that prevent normal activity

[1] Greatest surface diameter in mm.
[2] Defined as localized axillary, cervical or supraclavicular swelling or tenderness ipsilateral to the administration arm.
[3] Refer to the SoA for the definition of fever and the preferred location for temperature measurement.

10.3.5.3. Assessment of causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each unsolicited AE/SAE/AESI/device deficiency. The investigator will use clinical judgment to determine the relationship.
- A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

- For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.
- The investigator must review and provide an assessment of causality for each unsolicited AE/SAE and document this in the medical notes. There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to GSK.
- The investigator may change their opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.3.5.4. Assessment of outcomes

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

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

10.3.5.5. Follow-up of AEs, SAEs, AESIs, pregnancies or any other events of interest

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

After the initial AE/SAE/AESI/pregnancy or any other event of interest, the investigator is required to proactively follow each participant at subsequent visits/contacts.

All SAEs, and AESI (as defined in the Section 8.4.4), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.

Other nonserious AEs must be followed until Day 183 or until the participant is lost to follow-up.

Follow-up during the study

AEs/AESIs/SAE documented at a previous visit/contact and defined as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the end-of-study (Day 183) or the participant is lost to follow-up.

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

Follow-up of pregnancies

Pregnant participants will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK using the paper pregnancy follow-up report/electronic pregnancy report and the AE Report if applicable. Generally, the follow-up period does not need to be longer than 6 to 8 weeks after the estimated date of delivery.

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

Furthermore, the investigator must report any SAE occurring as a result of a post-study pregnancy that is considered by the investigator to be reasonably related to the study intervention, to GSK as described in the Section 10.3.5.7.

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

When additional SAE, AESI or pregnancy information is received after write access to the participant's eCRF is removed, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be sent to the study contact for reporting SAEs (see Section 8.4.3).

10.3.5.7. Reporting of SAEs, AESIs, and pregnancies

SAE reporting to GSK via an electronic data collection tool

- The primary mechanism for reporting an SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.

- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone.
- If the site during the course of the study or poststudy becomes aware of any serious, nonserious AEs, pregnancy exposure, related to any GSK product that is not part of the study design, they will report these events to GSK or to the concerned CA via the national spontaneous reporting system. These will be classified as spontaneous individual case safety reports (ICSRs).
- Contacts for SAE reporting can be found in Section 8.4.7.

SAE reporting to GSK via paper data collection tool

- Email/facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the medical monitor.
- In rare circumstances and in the absence of email/facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.
- Contacts for SAE reporting can be found in Section 8.4.7.

10.4. Appendix 4: Contraceptive and barrier guidance

10.4.1. Definitions

10.4.1.1. WOCBP

Women in the following categories are considered WOCBP (fertile):

- Adolescents of childbearing potential: Tanner stage ≥2 (post-thelarche) irrespective of the occurrence of menarche or following menarche.
- From the time of menarche until becoming postmenopausal unless permanently sterile (see below).

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

10.4.1.2. Women of non-childbearing potential (WONCBP)

Women in the following categories are considered WONCBP:

- Premenarchal: Tanner stage 1 (prepubertal).
- Permanently sterile due to one of the following procedures:
  a. Documented hysterectomy.
  b. Documented bilateral salpingectomy.
  c. Documented bilateral oophorectomy.

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

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

- Postmenopausal female.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

- A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
- Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. Contraception guidance

- Female participants of childbearing potential are eligible to participate if they agree to use a highly effective contraceptive method consistently and correctly according to the methods listed in GSK's list of highly effective contraceptive methods (Table 21).

Table 21 Highly effective contraceptive methods

Highly effective contraceptive methods that are user dependent[1] Failure rate of <1% per year when used consistently and correctly.

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation.
  • Oral.
  • Intravaginal.
  • Transdermal.

• Progestogen-only hormonal contraception associated with inhibition of ovulation.   • Injectable.

• Oral.
Highly effective methods that are user independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation.
• IUD.
• IUS.
• Bilateral tubal occlusion/ligation.
• Vasectomized partner. • A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP, and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
• Male partner sterilization prior to the female participant's entry into the clinical study, and this male is the sole partner for that participant. • The information on the male sterility can come from the site personnel's review of the participant's medical records; medical examination and/or semen analysis, or medical history interview provided by her or her partner.
• Sexual abstinence. • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant.

IUD = Intrauterine device; IUS = Intrauterine hormone-releasing system; WOCBP = Woman of childbearing potential.
[1] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

10.5. Appendix 5: Medical device AEs, ADEs, SAEs, SADEs, USADEs and device deficiencies: Definitions and procedures for recording, evaluating, follow-up, and reporting in medical device studies

- Both the investigator and the sponsor will comply with all local reporting requirements for medical devices.
- The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study. See Section 6.1.1 for the list of sponsor medical devices.

10.5.1. Definition of medical device AE and ADE

Medical device AE and ADE definition
• A medical device AE is any untoward medical occurrence, in a clinical study participant, users, or other persons, temporally associated with the use of study intervention whether or not considered related to the investigational medical device. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices.

• An ADE is defined as an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.5.2. Definition of medical device SAE, SADE, and USADE

A medical device SAE is any serious AEs that:
a. Led to death.
b. Led to serious deterioration in the health of the participant, that either resulted in: • A life-threatening illness or injury. The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. • A permanent impairment of a body structure or a body function. • Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. • Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function. • Chronic disease (MDR 2017/745).
c. Led to fetal distress, fetal death or a congenital abnormality or birth defect.
d. Is a suspected transmission of any infectious agent via a medicinal product.
SADE definition
• A SADE is defined as an ADE that has resulted in any of the consequences characteristic of an SAE. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
Unanticipated SADE (USADE) definition
• An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is defined as a serious ADE that by its nature, incidence, severity or outcome has not been identified in the current version of the IB (see Section 2.3).

10.5.3. Definition of device deficiency

Device deficiency definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequacy of the information supplied by the manufacturer.

10.5.4. Recording and follow-up of medical device AEs and/or SAEs and device deficiencies

10.5.4.1. Medical device AE, SAE, and device deficiency recording

- When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the AE/SAE/device deficiency form.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant identifier, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.
- If the site during the course of the study becomes aware of any serious, nonserious incident (including device deficiencies and malfunctions) related to any GSK product that is not part of the study design, they will report these events to GSK or to the concerned competent authorities (CA) via the national spontaneous reporting system. These will be classified as spontaneous ICSRs.

10.5.4.2. Assessment of intensity

See Section 10.3.5.2.

10.5.4.3. Assessment of causality

See Section 10.3.5.3.

10.5.4.4. Follow-up of medical device AE/SAE and device deficiency

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed form.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.5.5. Reporting of medical device SAEs

Medical Device SAE Reporting to GSK **via an Electronic Data Collection Tool**

- The primary mechanism for reporting an SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next table) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next table) or to the medical monitor by telephone.
- If the site during the course of the study or poststudy becomes aware of any serious, nonserious AEs, pregnancy exposure, related to any GSK device they will report these events to GSK or to the concerned CA via the national spontaneous reporting system. These will be classified as spontaneous ICSRs.
- Contacts for SAE reporting can be found in Section 8.4.7.

Medical device SAE reporting to GSK **via paper data collection tool**

- Email/Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the medical monitor.
- In rare circumstances and in the absence of email/facsimile equipment, notification by telephone is acceptable with a copy of the SAE paper data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE paper data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in Section 8.4.7.

10.5.6. Reporting of SADEs

SADE Reporting to GSK

Note: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency.
- The sponsor will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
- Contacts for SAE reporting can be found in Section 8.4.7.

10.5.7. Reporting of medical device deficiencies for associated person

Reporting to GSK
If an Associated Person (e.g., spouse, caregiver, site staff) experiences a device deficiency, the medical device deficiency information, and any associated AE/SAE information will be reported to GSK. The associated person will be provided with the authorization to contact physician letter. If follow-up information is required, authorization to contact physician (or other licensed medical practitioner) must be signed to obtain consent. • Medical device deficiencies that are not related to an AE or SAE should be reported via email to gsk-rd.complaints@gsk.com, using the medical device deficiency report form.

- If the medical device deficiency is related to a nonserious AE and not linked to an SAE, please send the medical device deficiency report form with details of the associated AE via email to gsk-rd.complaints@gsk.com only.
- If the device incident is linked to an SAE, please email the medical device deficiency report form, within 24 hours. See Section 8.4.7 for reporting.
- GSK will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.

10.6. Appendix 6: Protocol amendment history

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

Amendment 1 (16 May 2024)

Overall rationale for the Amendment

Following the feedback received from the Food and Drug Administration (FDA), the protocol has been amended to reflect the use of pausing criteria.

Summary of changes table of previous amendments:

Section # and title	Description of change	Brief rationale
8.3.6 Safety monitoring, committees, and study pausing criteria 8.3.6.1 Study pausing criteria 8.4.7 Contact information for reporting SAEs, AESIs, pregnancies and study pausing criteria	Study pausing criteria have been introduced. The role of the investigator in the monitoring of participants' safety has been clarified. Contact information for reporting study pausing criteria has been added.	To comply with the recommendations of the US FDA to define study pausing criteria.
8.3.1 Physical examination	Details of physical examination assessment at unscheduled site visits have been added.	To specify monitoring of participants' vital signs in case of suspected myocarditis or pericarditis.

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