CLINICAL STUDY PROTOCOL

Primary study Intervention(s)	BIO FLU SV MRNA (GSK4382276A)
Other study intervention(s)	CCI [redacted]
Study Identifier	217884 (FLU SV MRNA-002)
EU CT Number	2022-502308-66-00
IND number	29301
Approval Date	28 Aug 2023
Title	A Phase 1/2, randomized, dose-finding/dose-confirmation study to evaluate the reactogenicity, safety and immunogenicity of mRNA-based multivalent seasonal influenza vaccine candidates administered in healthy younger and older adults
Brief title	A study to find and confirm the dose and assess the safety, reactogenicity and immune response of a vaccine against influenza in healthy younger and older adults.
Sponsor	GlaxoSmithKline Biologicals S.A. Rue De L'Institut 89 1330 Rixensart Belgium
Sponsor signatory	Pascal Peeters, MD Senior Director, Clinical Project Lead

Medical monitor name and contact information will be provided in the local study contact information document.

PROTOCOL AMENDMENT 2 INVESTIGATOR AGREEMENT

I agree:

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

Hence, I:

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

Study identifier	217884 (FLU SV MRNA-002)
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Approval date	28 Aug 2023
Title	A Phase 1/2, randomized, dose-finding/dose-confirmation study to evaluate the reactogenicity, safety and immunogenicity of mRNA-based multivalent seasonal influenza vaccine candidates administered in healthy younger and older adults
Investigator name	_____
Signature	_____
Date of signature (DD Month YYYY)	_____

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 2	28 Aug 2023
Amendment 1	07 April 2023
Protocol	02 February 2023

Amendment 2 (28 Aug 2023)

This amendment is considered substantial based on the criteria defined in EU Clinical Trial Regulation No 536/2014 of the European Parliament and the Council of the European Union because it significantly impacts the safety of participants.

Overall rationale for the current amendment:

Following the first scheduled interim analysis (on reactogenicity, safety and immunogenicity data from Phase 1, up to Day 29 post-dosing), the protocol has been amended to include the doses selected for Phase 2, by the internal data review committee, as well as justification of dose selection.

LIST OF MAIN CHANGES IN THE PROTOCOL AND THEIR RATIONALE:

Section # and title	Description of change	Brief rationale
1.2. Schema; Figure 2. Study design overview. Phase 2	Figure updated according to sample size for Phase 2, and with Phase 2 interim analysis at Day 29.	Sample size was adjusted for Phase 2, and information for interim analysis at Day 29 was added.
2.3.3. Overall benefit-risk conclusion	Updated to include the safety, reactogenicity and immunogenicity conclusions from the Phase 1 part.	The benefit-risk profile was updated to include the conclusion from the first scheduled interim analysis of Phase 1 data.
4.1 Overall design	Added that participants completing the Phase 2 part will be offered the opportunity to participate in the extension study.	Participants completing the Phase 2 part of this study will be offered the opportunity to participate in the extension study.
4.1. Overall design; Table 7. List of study interventions for Phase 2 4.3. Justification of dose 4.3.2. Dose selection for Phase 2 6.1 Study interventions administered; Table 9. Study interventions administered. Phase 2	Selected dose levels (and study interventions) and study groups are now described	Rationale for dose levels and study groups is provided in Section 4.3 Justification for dose.
4.1. Overall design 6.3. Assignment to study intervention 8.2.3. Immunological read-outs	Updated according to the sample size proposed in Phase 2.	The initial sample size for Phase 2 was based on a conservative value of 0.55 standard deviation. The Phase 1 part indicated that 0.5

Section # and title	Description of change	Brief rationale
9.5.2. Sample size determination for Phase 2		could be used and the sample size was adjusted accordingly.
5.2.1. Medical conditions 10.6.1. Specific requirements for South Africa	Information regarding HIV testing of participants from South Africa before enrollment was added.	To align with South African Health Products Regulatory Authority request.
8.3.4. Myocarditis and pericarditis assessment and definitions	Further details added from the already referenced Brighton Collaboration guidance on myocarditis/pericarditis investigation (SPEAC, 2022) to clarify the specific clinical data needed in the diagnostic procedures of myocarditis/pericarditis	To further clarity the diagnostic procedures of myocarditis/pericarditis in Phase 2.
8.3.7.2. Study holding rules; Table 13. Study holing rules for Phase 1, Table 14. Study holding rules for Phase 2	Holding rule 2a for Phase 2 revised to include "same solicited AE lasting 2 consecutive days (48 hours) or more as Grade 3." Holding rule 2a and 2b for Phase 2 thresholds changed from ≥2 to ≥5% (and ≥2). To accommodate these changes the holding rule table was split in two.	During Phase 1 it was observed that the endpoint for holding rule 2a was related to transient self-limiting events not considered relevant for justifying a study hold and the endpoint was therefore revised to events lasting 2 consecutive days or more. Thresholds changed to account for group size difference between Phase 1 (n=24 per group) and Phase 2 (n=120 per group).
8.4.1. Time period and frequency for collecting AE, SAE, and other safety information	Clarification of the role of the investigator in notifying the sponsor regarding AEs or SAEs after conclusion of study participation.	Updated to clarify the role of the investigator in notifying the sponsor regarding AEs or SAEs after conclusion of study participation.
9.4.1. Sequence of interim and other planned analyses	Updated language regarding access to group data during Phase 2 interim analysis.	To provide further clarity on blinding.
10.3.3. Solicited events 10.3.4 Unsolicited AE	Added language regarding eDiary process	To comply with CBER's non-hold recommendations

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
Ab	Antibody
ADE	Adverse device effect
AE	Adverse event
AESI	Adverse events of special interest
BLRM	Bayesian Logistic Regression Model
BMI	Body mass index
CCI	[redacted]
CI	Confidence interval
CCI	[redacted]
CSR	Clinical study report
ECG	***Electrocardiogram***
eCRF	Electronic case report form
CCI	[redacted]
EMA	European Medicines Agency
EoS	End of study
ES	Exposed set
FDA	Food and Drug Administration, United States of America
FSFV	First subject first visit
FTiH	First-time in human
GCP	Good clinical practices
GMI	Geometric mean increase

Abbreviation	Definition
GMT	Geometric mean titers
CCI	[redacted]
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council on Harmonisation
ICSR	Individual case safety reports
iDRC	Internal Data Review Committee
IEC	Independent ethics committee
CCI	[redacted]
IRB	Institutional review board
iSRC	Internal Safety Review Committee
LLOQ	Lower level of quantification
LSLV	Last Subject Last Visit
MAE	Medically attended event
CCI	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
MN	Microneutralization
CCI	[redacted]
OA	Older adult
CCI	[redacted]
PI	Prescribing Information

Abbreviation	Definition
pIMD	Potential immune-mediated disease
PPS	Per Protocol set
PRO	Patient-related outcomes
PT	Preferred term
QTL	Quality tolerance limit
SADE	Serious adverse device effect
SAE	Serious adverse event
SBIR	Source data Base for Internet Randomization
SCR	Seroconversion rate
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SPR	Seroprotection rate
SRT	***Safety Review Team***
CCI [redacted]	
USADE	Unanticipated serious adverse device effect
VAERS	Vaccine adverse event reporting system
CCI [redacted]	
WOCBP	Woman of childbearing potential
WONCBP	Woman of non-childbearing potential
YA	Younger adult

Term	Definition
Adverse event of special interest	An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them. Depending on the nature of the event, rapid communication by the trial sponsor to other parties may also be needed (e.g., regulators) [CIOMS, 2021].
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 a single-blind study, the investigator(s) and/or their staff are aware of the intervention assignment, but the participant is not. 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 (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.

Term	Definition
Combination product	Combination product comprises any combination of • drug • device • biological product Each drug, device and biological product included in a combination product is a constituent part.
eDiary	Electronically registered 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 which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.
Immunological correlate of protection	A correlate of risk that has been validated to predict a certain level of protection from the targeted endpoint.
Intercurrent medical conditions	Intercurrent medical conditions are defined as medical conditions that occur after vaccine administration and either preclude observation of the outcome of interest (immunogenicity/efficacy endpoint) or affect its interpretation (by altering the immune response to vaccination or altering the initial immune status of the participant).
Intervention number	A number identifying an intervention to a participant, according to intervention allocation.
Investigational medicinal/vaccine product	An IMP is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, 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. Medicinal products with a marketing authorization are IMPs when they are to be used as the test substance, reference substance, or comparator in a clinical study, provided the requirement(s) in the definition is/are met.

Term	Definition
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.
Medically attended event	An AE that results in an unscheduled visit to a medical professional (e.g., physician's office visits, emergency room visits or hospitalization).
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)/control). Synonym: subject.
Participant number	A unique identification number assigned to each participant who consents to participate in the study.
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).
Study intervention	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a participant.
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 study procedures are planned as compared to other participants or a group of participants who share a common characteristic (e.g., ages, vaccination schedule, etc.) at the time of enrollment.

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol title:

A Phase 1/2, randomized, dose-finding/dose-confirmation study to evaluate the reactogenicity, safety and immunogenicity of mRNA-based multivalent seasonal influenza vaccine candidates administered in healthy younger and older adults.

Brief title:

A Phase 1/2, randomized, dose-finding/dose-confirmation study to evaluate how healthy younger and older adults respond to mRNA-based seasonal influenza vaccine candidates.

Rationale: Refer to Section 2.1.

Objectives, Endpoints and Estimands: Refer to Section 3.

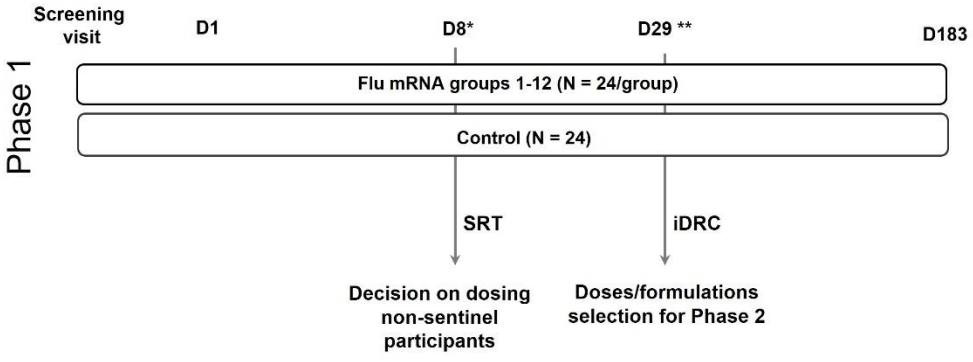
Overall Design: Refer to Section 4.1.

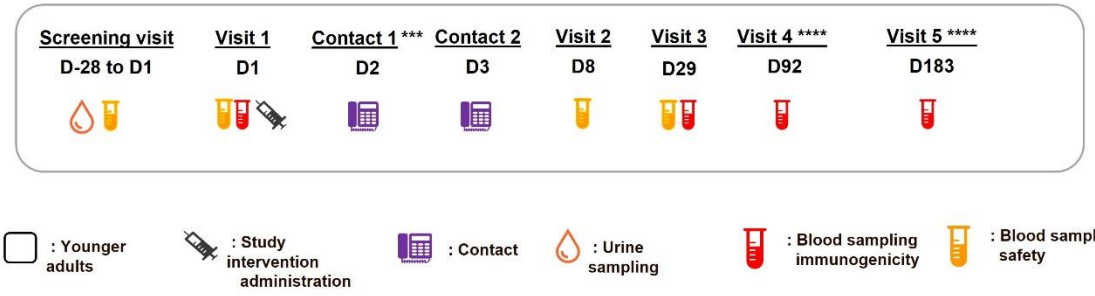
Number of Participants: Refer to Section 9.5.

Data Monitoring/Other Committee: Refer to Section 10.1.6.

1.2. Schema

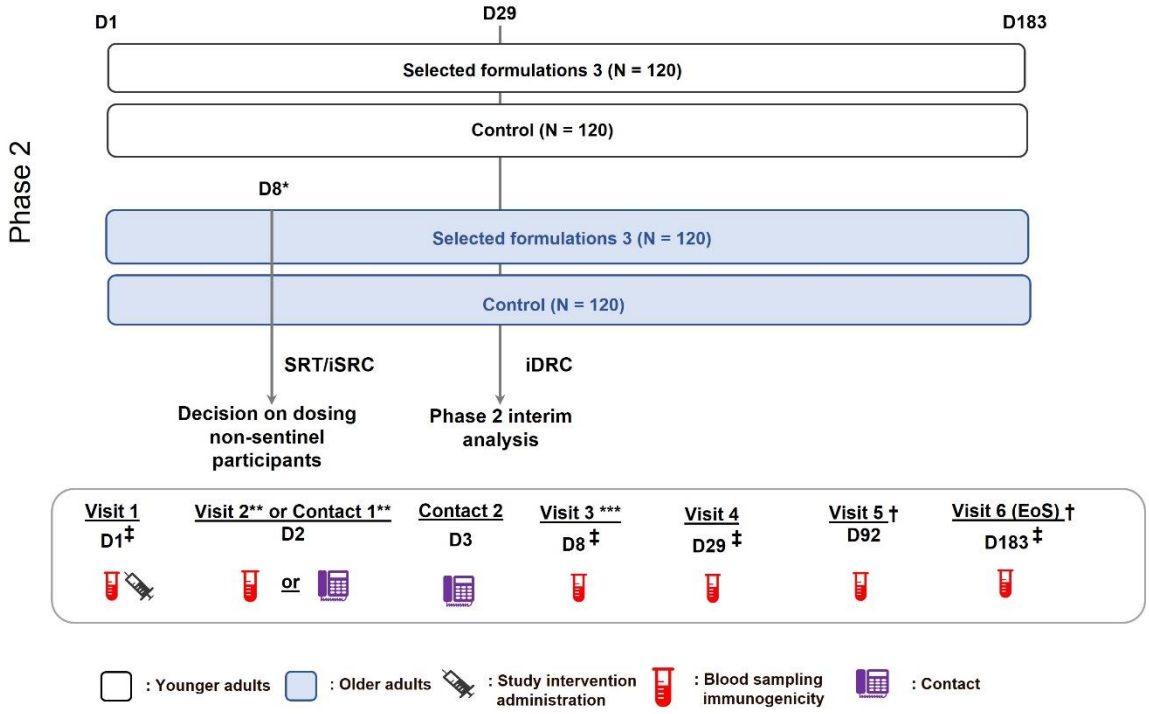
Figure 1 Study design overview. Phase 1





D: day; ***SRT:*** safety review team; iDRC: internal data review committee; N: number of participants
Control: licensed influenza vaccine. Refer to Section 4.1 for more information.
* Safety review of 7-days post-dosing (Day 8) data of sentinel participants by ***SRT***. Refer to Section 8.3.7.1 for details.
** Selection of doses/formulations for Phase 2 by the iDRC. Refer to Section 4.3 for more information.
*** Contact 1 will only be applicable for the first 5 participants per group. Remaining Phase 1 participants will not have any contact at Day 2.
**** Visit 4 and 5 will be replaced by a Contact if participant has received the standard of care vaccination against seasonal flu after Day 29 and prior to this visit and did not report any adverse events that would require physical examination on site.

Figure 2 Study design overview. Phase 2



D: day; EoS: end of study; ***SRT:*** safety review team; iSRC: internal safety review committee; N: number of participants.
Control: licensed influenza vaccine. Refer to Section 4.1 for more information.
* Safety review of 7-days post-dosing (Day 8) data of sentinel OA participants by ***SRT***/iSRC. Refer to Section 8.3.7.1 for details.
** Contact 1 will only be applicable for the first 5 participants in OA groups. Visit 2 (Day 2) will only be applicable for participants in the exploratory immunogenicity subset in Phase 2. Remaining Phase 2 participants will not have any contact or visit at Day 2.
*** Visit 3 (Day 8) will be replaced by a Contact for all non-subset participants in Phase 2.
† Visit 5 and 6 will be replaced by a Contact if participant has received the standard of care vaccination against seasonal flu after Day 29 prior to this visit and did not report any adverse events that would require physical examination on site.
‡ Additional blood samples will be collected for a subset of participants in Phase 2.

1.3. Schedule of activities (SoA)

Table 1 Schedule of activities (SoA). Phase 1

Type Of Contact	Screening Visit	Visit 1	Contact 1*	Contact 2	Visit 2	Visit 3	Visit 4‡	Visit 5‡	Notes
Timepoints	**Day -28 to Day 1**	**Day 1**	**Day 2**	**Day 3**	**Day 8**	**Day 29**	**Day 92**	**Day 183**	
Informed consent	●[a]								See Section 10.1.3 for details
Inclusion and exclusion criteria	●	○[a]							Check clinical status before randomization and/or administration of study intervention. See Sections 5.1 and 5.2 for Inclusion and Exclusion criteria
Collect demographic data	●								See Section 8.1.1 for details
Medical and vaccination history	●	○[a]							See Section 8.1.2 for details
Physical examination	●	●[a]			○	○	○	○	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 details
Urine pregnancy test (only for female participants of childbearing potential)	●	●[a]							Serum pregnancy test can be done as per local requirements if time allows. See Section 8.3.6 for details
Randomization		○[a]							Country, study, center and flu vaccination history in the past 2 years will be used as minimization factor. Sentinel status will be a stratification factor. See Section 6.3 for details.
Check contraindications, warnings, and precautions to vaccination		○[a]							See Section 8.3.3 for details
Check criteria for temporary delay for enrollment and/or study intervention administration		○[a]							See Section 5.5 for details
Study group and intervention number allocation		●[a]							See Section 6.3 for details

Type Of Contact	Screening Visit	Visit 1	Contact 1*	Contact 2	Visit 2	Visit 3	Visit 4‡	Visit 5‡	Notes
Timepoints	**Day -28 to Day 1**	**Day 1**	**Day 2**	**Day 3**	**Day 8**	**Day 29**	**Day 92**	**Day 183**	
Body temperature before study intervention administration		●[a]							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 axillary. See Section 8.3.2 for details
Administration of study intervention		●							See Section 6.1 for details
Recording of administered study intervention number		●							
Post-dose observation period		○							See Section 6.1 for details
Distribution of participant card		○							See Section 8.4.8 for details
Check participant's device compatibility for eDiary data collection	○	○							See Section 8.1.3 for details
Training and installing/assigning eDiary		○							See Section 8.1.3 for details
Review of eDiary data			○	○	○	○			Reporting of solicited events (Day 1-Day 7 post-dosing) [b] Reporting of unsolicited adverse events (Day 1-Day 28 post-dosing) [b] Completion of [redacted] (Day 3 and Day 7 post-dosing) [b] See Sections 8.10 and 8.4.1 for details
Return/uninstalling of eDiary						○			See Section 10.3.5.1 for details
Laboratory assessment									
Urine sampling for routine safety panel All participants	●								Volume of urine sample will be defined as per local practice. See Section 8.2.1 for details
Blood sampling for antibody determination (~30 mL)		○ [a]				○	○ **	○ **	For this assessment, serum has to be isolated from blood. See Section 8.2.1 for details

Type Of Contact	Screening Visit	Visit 1	Contact 1*	Contact 2	Visit 2	Visit 3	Visit 4‡	Visit 5‡	Notes
Timepoints	**Day -28 to Day 1**	**Day 1**	**Day 2**	**Day 3**	**Day 8**	**Day 29**	**Day 92**	**Day 183**	
Blood sampling for routine safety panel (~10 mL)	●	●[a]			●	●			If screening occurs within 3 days (Day -3 to Day -1) before Visit 1, the results of safety lab assessments from screening can be used as baseline. Volume of the blood drawn will vary depending on local lab requirements. See Section 8.2.1 for details
Safety assessments									
Record any concomitant vaccinations	●	●	●	●	●	●	●	●	See Section 6.9 for details
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●	●	●	●	●	●	See Section 8.4.1 for details
Record AEs leading to withdrawal from study		●	●	●	●	●	●	●	See Section 8.4.1 for details
Recording of non-serious adverse events		●	●	●	●	●			See Section 8.4.1 for details
Recording of MAEs, SAEs, AESIs and pregnancies		●	●	●	●	●	●	●	See Section 8.4.1 for details
Record any concomitant medications		●	●	●	●	●	●	●	See Section 6.9 for details
Record any intercurrent medical conditions		●	●	●	●	●	●	●	See Section 9.2 for details
Study conclusion								●	See Section 10.1.10 for details

● 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
[a] Is used to indicate a study procedure to be performed prior to study intervention administration.
[b] Is used to indicate a study procedure recorded in eDiary.
* Contact 1 (Day 2) will only be applicable for the sentinel participants in Phase 1. Remaining Phase 1 participants will not have a visit or contact at Day 2.
** Blood samples should only be collected for participants who did not receive a standard of care vaccination against seasonal flu since their enrollment into the study.
‡ Visit 4 and 5 will be replaced by a Contact if participant has received the standard of care vaccination against seasonal flu after Day 29 and prior to this visit and did not report any adverse events that would require physical examination on site.
Contact may be via telephone, SMS, email, video-telephone/telemedicine or other means, depending on local best practice.

Table 2 Schedule of activities (SoA). Phase 2

Type Of Contact	Visit 1	Visit 2*	Contact 1**	Contact 2	Visit 3†	Visit 4	Visit 5‡	Visit 6‡	Notes
Timepoints	Day 1	Day 2	Day 2	Day 3	Day 8	Day 29	Day 92	Day 183	
Informed consent	●[a]								See Section 10.1.3 for details
Inclusion and exclusion criteria	●[a]								Check clinical status before randomization and/or administration of study intervention. See Sections 5.1 and 5.2 for Inclusion and Exclusion criteria
Collect demographic data	●								See Section 8.1.1 for details
Medical and vaccination history	●[a]								See Section 8.1.2 for details
Physical examination	●[a]	○			○	○	○	○	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 details
Urine pregnancy test (only for female participants of childbearing potential)	●[a]								Serum pregnancy test can be done as per local requirements if time allows. See Section 8.3.6 for details
Randomization	○[a]								Country, study, center and flu vaccination history in the past 2 years will be used as minimization factor. Age group and sentinel status will be stratification factors. See Section 6.3 for details.
Check contraindications, warnings, and precautions to vaccination	○[a]								See Section 8.3.3 for details
Check criteria for temporary delay for enrollment and/or study intervention administration	○[a]								See Section 5.5 for details
Study group and intervention number allocation	●[a]								See Section 6.3 for details

Type Of Contact	Visit 1	Visit 2*	Contact 1**	Contact 2	Visit 3†	Visit 4	Visit 5‡	Visit 6‡	Notes
Timepoints	Day 1	Day 2	Day 2	Day 3	Day 8	Day 29	Day 92	Day 183	
Body temperature before study intervention administration	●[a]								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 axillary. See Section 8.3.2 for details
Administration of study intervention	●								See Section 6.1 for details
Recording of administered study intervention number	●								
Post-dose observation period	○								See Section 6.1 for details
Distribution of participant card	○								See Section 8.4.8 for details
Check participant's device compatibility for eDiary data collection	○								See Section 8.1.3 for details
Training and installing/assigning eDiary	○								See Section 8.1.3 for details
Review of eDiary data		○	○	○	○	○			Reporting of solicited events (Day 1-Day 7 post-dosing) [b] Reporting of unsolicited adverse events (Day 1-Day 28 post-dosing) [b] Completion of [redacted] Day 3 and Day 7 post-dosing) [b] See Sections 8.10 and 8.4.1 for details
Return/uninstalling of eDiary						○			See Section 10.3.5.1 for details

Type Of Contact	Visit 1	Visit 2*	Contact 1**	Contact 2	Visit 3†	Visit 4	Visit 5‡	Visit 6‡	Notes
Timepoints	**Day 1**	**Day 2**	**Day 2**	**Day 3**	**Day 8**	**Day 29**	**Day 92**	**Day 183**	
Laboratory assessment									
Blood sampling for antibody determination	○ [a]					○	○ ***	○ ***	For this assessment, serum has to be isolated from blood. See Section 8.2.1 for details For YA non-subset participants in Phase 2, the individual volume per visit will be 30 mL For OA non-subset participants in Phase 2, the individual volume per visit will be 10 mL. For YA and OA subset participants in Phase 2 the individual volume per visit will be 10 mL.
Blood sampling for CMI response (PBMC) Subset of Phase 2 participants	○ [a]				○			○ ***	Volume to be collected: Visit 1 and Visit 6: ~40 mL per visit Visit 3: ~60 mL See Section 8.2.1 for details
Blood sampling for cell-produced cytokine response (whole blood, CCI tubes) (~4 mL) Subset of Phase 2 participants	○ [a]				○				For CCI sample collection will be limited to selected sites. See Section 8.2.1 for details
Blood sampling for innate response (~5 mL) Subset of Phase 2 participants	○ [a]	○			○				For this assessment, plasma should be isolated from blood. See Section 8.2.1 for details
Blood sampling for humoral immunity for circulating drift variants of the vaccine subtypes not used in the vaccine, for MN and potential additional exploratory assays (~20 mL) Subset of Phase 2 participants	○ [a]					○		○ ***	For this assessment, serum should be isolated from blood. See Section 8.2.1 for details
Safety assessments									
Record any concomitant vaccinations	●	●	●	●	●	●	●	●	See Section 6.9 for details

Type Of Contact	Visit 1	Visit 2*	Contact 1**	Contact 2	Visit 3†	Visit 4	Visit 5‡	Visit 6‡	Notes
Timepoints	Day 1	Day 2	Day 2	Day 3	Day 8	Day 29	Day 92	Day 183	
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●	●	●	●	●	●	See Section 8.4.1 for details
Record AEs leading to withdrawal from study	●	●	●	●	●	●	●	●	See Section 8.4.1 for details
Recording of non-serious adverse events	●	●	●	●	●	●			See Section 8.4.1 for details
Recording of MAEs, SAEs, AESIs and pregnancies	●	●	●	●	●	●	●	●	See Section 8.4.1 for details
Record any concomitant medications	●	●	●	●	●	●	●	●	See Section 6.9 for details
Record any intercurrent medical conditions	●	●	●	●	●	●	●	●	See Section 9.2 for details
Study conclusion								●	See Section 10.1.10 for details

● Is used to indicate a study procedure that requires documentation in the individual CRF/eCRF
○ Is used to indicate a study procedure that does not require documentation in the individual CRF/eCRF
[a] Is used to indicate a study procedure to be performed prior to study intervention administration.
[b] Is used to indicate a study procedure recorded in eDiary.
* Visit 2 (Day 2) will only be applicable for participants in the exploratory immunogenicity subset in Phase 2. Remaining Phase 2 participants will not have a visit at Day 2.
** Contact 1 (Day 2) will only be applicable for the sentinel OA participants in Phase 2. Remaining Phase 2 participants will not have a contact at Day 2.
*** Blood samples should only be collected for participants who did not receive a standard of care vaccination against seasonal flu since their enrollment into the study.
† Visit 3 (Day 8) will be replaced by a Contact for all non-subset participants in Phase 2 and if participant did not report any adverse events that would require physical examination on site.
‡ Visit 5 and 6 will be replaced by a Contact if participant has received the standard of care vaccination against seasonal flu after Day 29 and prior to this visit and did not report any adverse events that would require physical examination on site.
Contact may be via telephone, SMS, email, video-telephone/telemedicine or other means, depending on local best practice.

Table 3 Intervals between study visits. Phase 1

Interval*	Planned visit interval	Allowed interval range
Screening Visit** → Visit 1	1-28 days	1 – 28 days
Visit 1 → Contact 1***	1 day	1 day
Visit 1 → Contact 2	2 days	2-3 days
Visit 1 → Visit 2	7 days	6-8 days
Visit 1 → Visit 3	28 days	28-35 days
Visit 1 → Visit 4‡	91 days	84-98 days
Visit 1 → Visit 5‡	182 days	180-210 days

* Interval is computed as the difference between 2 dates

** Screening Visit is planned for participants enrolled in Phase 1 and needs to be performed within 28 days before Visit 1, with sufficient time to receive/review the hematology, biochemistry, HbA1c and urinalysis results. When applicable, a re-screening visit (including blood and urine sample collection, physical examination and re-checking of inclusion/exclusion criteria) may be scheduled at any time (but only once to assess eligibility) before Visit 1. In this case, all screening procedures must be completed within 28 days before Visit 1 (Day 1). Only laboratory results from the re-screening visit, if it occurs, will be taken into consideration. The participant can only be randomized once the investigator receives the results and confirms the eligibility criteria.

*** Contact 1 (Day 2) will only be applicable for the sentinel participants in Phase 1. Remaining Phase 1 participants will not have a visit or contact at Day 2.

‡ Visit 4 and 5 will be replaced by a Contact if participant has received the standard of care vaccination against seasonal flu after Day 29 and prior to this visit and did not report any adverse events that would require physical examination on site.

Table 4 Intervals between study visits. Phase 2

Interval*	Planned visit interval	Allowed interval range
Visit 1 → Visit 2**	1 day	1 day
Visit 1 → Contact 1***	1 day	1 day
Visit 1 → Contact 2	2 days	2-3 days
Visit 1 → Visit 3†	7 days	6-8 days
Visit 1 → Visit 4	28 days	28-35 days
Visit 1 → Visit 5‡	91 days	84-98 days
Visit 1 → Visit 6‡	182 days	180-210 days

* Interval is computed as the difference between 2 dates

** Visit 2 (Day 2) will only be applicable for participants in the exploratory immunogenicity subset in Phase 2. Remaining Phase 2 participants will not have a visit at Day 2.

*** Contact 1 (Day 2) will only be applicable for the sentinel OA participants in Phase 2. Remaining Phase 2 participants will not have a contact at Day 2.

† Visit 3 (Day 8) will be replaced by a Contact for all non-subset participants in Phase 2 and if participant did not report any adverse events that would require physical examination on site.

‡ Visit 5 and 6 will be replaced by a Contact if participant has received the standard of care vaccination against seasonal flu after Day 29 and prior to this visit and did not report any adverse events that would require physical examination on site.

2. INTRODUCTION

2.1. Study rationale

Annual influenza vaccination is currently the most effective mean of controlling influenza and preventing its complications and mortality [WHO, 2018].

Influenza viruses constantly change their surface glycoproteins that are the targets of most immune responses, allowing them to escape pre-existing immunity, a process called antigenic drift. Therefore, seasonal influenza vaccines must be reformulated and re-administered on an annual basis [WHO, 2021].

GSK and CureVac are developing a quadrivalent seasonal influenza vaccine based on mRNAs encoding the genetic sequences of 4 CCI [redacted], encapsulated in lipid nanoparticles. The vaccine is based on CureVac's second-generation mRNA backbone and modified nucleotides (i.e., N1-methyl-pseudouridine [N1mΨ]) which together are expected to have increased immunogenicity and lower reactogenicity [Stuart, 2021] compared to the mRNA platform used in the CVnCoV study [Kremsner, 2021]. Three clinical studies using the second-generation mRNA backbone (2 of them using modified nucleotides) have provided reactogenicity, safety and immunogenicity data to support the design of the current Phase 1/2 study:

- CCI [redacted] was a CureVac-sponsored dose-escalation Phase 1 study in healthy younger adults (YAs) and older adults (OAs). The study evaluated a multivalent seasonal influenza mRNA investigational vaccine based on unmodified nucleotides. Safety and reactogenicity data showed the vaccine candidate to be generally well tolerated with no safety concerns observed across all tested dose levels CCI [redacted] Refer to IB for more information.
- FLU SV MRNA-003 is an ongoing GSK-sponsored dose-escalation Phase 1 study in healthy YAs and OAs. The study is evaluating a monovalent influenza mRNA investigational vaccine based on modified nucleotides. Safety and reactogenicity data show the investigational vaccine to be generally well tolerated with no safety concerns observed across all tested dose levels CCI [redacted] Refer to IB for more information.
- CV2 SARS-COV2-012 BST is a GSK-sponsored dose-escalation Phase 1 study in healthy YAs and OAs. The study is evaluating a COVID-19 investigational vaccine based on modified nucleotides. Safety and reactogenicity data show the investigational vaccine to be generally well tolerated with no safety concerns observed across all tested dose levels CCI [redacted]). Refer to IB for more information.

In the current Phase 1/2 study, the safety, reactogenicity and immunogenicity of quadrivalent seasonal influenza investigational study interventions will be evaluated. The study consists of an exploratory dose-finding part (Phase 1) and dose-confirmation part (Phase 2). All study interventions will be based on the second-generation mRNA backbone and modified nucleotides. The data generated in Phase 1 ***(Refer to the IB for***

more information) will be used to determine the study interventions in Phase 2. The investigational study interventions in Phase 1 and Phase 2 will be compared to licensed influenza vaccines.

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, 2017].

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 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 active controls can be found in the respective Summary of Product Characteristics (SmPC) or Prescribing Information (PI).

As for any vaccine, administration site (e.g., pain, swelling, redness) and systemic (e.g., fever, fatigue, headache, myalgia) post-dosing events may occur within the first 3 days of study intervention administration, and are anticipated to resolve within a few days of onset.

2.3.1. Risk assessment

Potential risk	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 non-serious. Serious allergic reactions, including anaphylaxis, are usually very rare [McNeil, 2019]. The US Vaccine Safety Datalink 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 flu vaccines.	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 latex, polyethylene glycol, egg protein and aminoglycoside antibiotics) will be excluded from study participation. All participants will be observed for a specified period following dosing (60 minutes for Phase 1; 30 minutes for YA and 60 minutes for OA participants in Phase 2). 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	Participants with a history of, or uncontrolled, neurological disorders or seizures, including Bell's palsy, will be excluded from the study enrollment. Moreover, pIMDs including Bell's palsy will be collected as AESIs.

Potential risk	Summary of data/rationale for risk	Mitigation strategy
	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 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	

Potential risk	Summary of data/rationale for risk	Mitigation strategy
	still not completely understood, Bell's palsy is proposed as an important potential risk for this candidate vaccine.	
Guillain-Barré Syndrome (GBS)	The risk window of GBS is in the first 6 weeks post-vaccination. The estimated risk of GBS is 1 -to 2 cases per million vaccinations. 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 GBS. The estimated risk of GBS after influenza has been reported to be 17.2 cases per 1 million patients hospitalized with influenza. Furthermore, a study in Norway during the 2009 pandemic (H1N1) influenza found that the risk of GBS after influenza infection was higher than the relative risk for pH1N1 vaccination [Babazadeh, 2019]. Despite the small observed increased risk of GBS after influenza vaccination, evidence is growing in support of an apparent larger benefit of vaccination in the context of population health [Vellozzi, 2014]. 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*	Participants with a history of, or uncontrolled, neurological disorders or seizures, including GBS, will be excluded from the study enrollment. Moreover, pIMDs including GBS will be collected as AESIs

Potential risk	Summary of data/rationale for risk	Mitigation strategy
	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 after the procedure. The decision to dose the participant will be dependent on the clinical judgment of the investigator.

Potential risk	Summary of data/rationale for risk	Mitigation strategy
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.

Note: Myocarditis and pericarditis are currently not considered as important potential risks for this vaccine candidate as review of published literature has not identified evidence to consider myocarditis/pericarditis as an mRNA vaccine class-effect and the patho-mechanism is still unknown. However, these are considered as AESIs to further characterize the safety profile of the vaccine. In line with this, measures described in Section 8.3.4 have been included in the study protocol to closely monitor potential cases.

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. Considering the measures to minimize the risk to participants in this Phase 1/2 clinical study and given the accumulation of favorable safety/immunogenicity data from the FLU SV MRNA-003 (217895), safety data from CV2 SARS-COV2-012 BST (***218595***) ***studies, as well as the data presented as interim analysis up to Day 29 post-dosing (on reactogenicity, safety and immunogenicity of the vaccine candidates from Phase 1) for this study***, ***the anticipated benefit-risk profile for the seasonal mRNA investigational vaccine candidates remain positive to proceed with the Phase 2 part of the study***. Refer to ***the*** IB for more information.

3. OBJECTIVES, ENDPOINTS AND ESTIMANDS

Table 5 Objectives and endpoints

Objectives	Endpoints (population summary)
	Co-primary
To evaluate the safety and reactogenicity profile of the investigational study intervention	Solicited events*: • Occurrence of solicited administration site and systemic events within 7 days (i.e., from Day 1 to Day 7 included) of study intervention administration (percentage of participants). Unsolicited AEs*: • Occurrence of unsolicited AEs within 28 days (i.e., from Day 1 to Day 28 included) after study intervention administration (percentage of participants). SAEs*, AESI* and MAEs: • Occurrence of SAEs within 6 months (i.e., from Day 1 to Day 183) after study intervention administration (percentage of participants) • Occurrence of AESIs within 6 months (i.e., from Day 1 to Day 183) after study intervention administration (percentage of participants) • Occurrence of MAEs within 6 months (i.e., from Day 1 to Day 183) after study intervention administration (percentage of participants).

Objectives	Endpoints (population summary)
	For participants in **Phase 1:** Safety laboratory**:** • Shift from a non-clinically significant laboratory value on Day 1 (pre-dose) to a clinically significant abnormal laboratory value on Day 8 (post-dose) and/or Day 29 (post-dose) for hematology and clinical chemistry (percentage of participants).
To evaluate the humoral immune response induced by the investigational study intervention	• CCI antibody titer at Day 29 (GMT) • Fold increase in CCI antibody titer from Day 1 to Day 29 (GMI) • CCI seroconversion from Day 1 to Day 29 (SCR) • CCI seroprotection at Day 1 and Day 29 (SPR) • CCI antibody titer at Day 29 (GMT) • Fold increase in CCI antibody titer from Day 1 to Day 29 (GMI) • CCI seroconversion from Day 1 to Day 29 (SCR†)
Secondary	
To evaluate the humoral immune response induced by the investigational study intervention	• CCI antibody titer at Day 92 and Day 183 (GMT) • Fold increase in CCI antibody titer from Day 1 to Day 92 (GMI) • Fold increase in CCI antibody titer from Day 1 to Day 183 (GMI) • CCI seroprotection at Day 183 (SPR†) • CCI antibody titer at Day 92 and Day 183 (GMT) • Fold increase in CCI antibody titer from Day 1 to Day 92 (GMI) • Fold increase in CCI antibody titer from Day 1 to Day 183 (GMI)
Tertiary	
CCI [redacted]	

Objectives	Endpoints (population summary)
CCI [redacted]	

Endpoints are designed for all the participants, unless indicated otherwise in the table.
AE: adverse event; SAE: serious adverse event; AESI: adverse events of special interest; MAE: medically attended event; SCR: seroconversion rate; SPR: seroprotection rate; CCI [redacted] GMI: geometric mean increase; GMT: geometric mean titers; MN: microneutralization; CCI [redacted]
* Refer to Section 8.4.1 for the list of safety events and timeframe for collection.
† Refer to Section 9.3.2 for definition of SCR and SPR.

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

4. STUDY DESIGN

4.1. Overall design

Refer to Figure 1 and Figure 2 (Section 1.2) for the overview of study design.

- Multi-country, multi-center.
- Self-contained.
- All study interventions are administered as single-dose intramuscularly (IM).
- Active control:

CCI [redacted]

- Intended duration of the study per participant: Up to 7 months for participants enrolled in Phase 1 (screening period included) and 6 months for participants enrolled in Phase 2 of the study.
- Aspects of data collection: blood samples, safety events, CCI [redacted].
- Method of data collection:
  - Standardized electronic Case Report Form (eCRF)
  - Solicited AEs, the occurrence of unsolicited AEs and responses to CCI [redacted] will be collected using an electronic Diary (eDiary); participants, with support from the site, may install the eDiary application on their own personal, handheld device (e.g., mobile phone, tablet) or the site may provide a device that is pre-programmed with the eDiary.
- Safety monitoring: the review of safety data will be performed by an internal Safety Review Team (***SRT***) and internal Safety Review Committee (iSRC). Refer to Section 8.3.7.1 for more information on safety monitoring strategy applicable to this study and Section 10.1.6 for ***SRT*** and iSRC composition and role.

- Dose selection for Phase 2: refer to Section 4.3.2 for detailed information on dose selection by an internal Data Review Committee (iDRC) and Section 10.1.6 for iDRC composition and role.

Phase 1:

- Participants aged 18-50 years.
- 13 groups enrolled in parallel (12 mRNA groups and 1 control group), detailed in Table 6.
- Approximate number of participants: 312 (24 participants per group).
- Blinding: single-blind. Refer to Section 6.4 for more information on blinding.
- Study interventions administered in Phase 1 will be manufactured as separate components and mixed at site by the site staff/pharmacist based on the scheme provided in the Table 6, before dosing each participant. This approach will only be applicable in the Phase 1 part.

Table 6 Potential study interventions composition (Phase 1)

Study groups	Study interventions*	CCI [redacted]
Flu mRNA_1_1	F2C22C/DL001Z	
Flu mRNA_1_2	F2B22A/DL001Z	
Flu mRNA_1_3	F2B22B/DL001Z	
Flu mRNA_1_4	F2B22C/DL001Z	
Flu mRNA_1_5	F2B22D/DL001Z	
Flu mRNA_1_6	F2B22E/DL001Z	
Flu mRNA_1_7	F2F22A/DL001Z	
Flu mRNA_1_8	F2F22B/DL001Z	
Flu mRNA_1_9	F2F22C/DL001Z	
Flu mRNA_1_10	F2F22D/DL001Z	
Flu mRNA_1_11	F2F22E/DL001Z	
Flu mRNA_1_12	F2F22F/DL001Z	
Control	CCI [redacted]	

CCI [redacted]

* Strains used to design study interventions are based on WHO recommendation for influenza virus vaccine composition for the 2022-2023 NH season.
** CCI [redacted] GSKVx000000034792; CCI [redacted]: GSKVx000000040033; CCI [redacted]: GSKVx000000034794; CCI [redacted]: GSKVx000000034795; CCI [redacted]: GSKVx000000034796; CCI [redacted]: GSKVx000000034797; CCI [redacted]: GSKVx000000034798; CCI [redacted]: GSKVx000000039711. Refer to Section 4.3 for information on selection of doses and combinations and Section 6.1 for details on study interventions.

Phase 2:

- Participants aged 18-64 and 65-85 years.
- 8 groups enrolled in parallel (3 mRNA groups and 1 control group for each age range), Table 7.
- Approximate number of participants: ***960*** (***120*** participants per group).
- Blinding: observer-blind. Refer to Section 6.4 for more information on blinding.
- CCI [redacted]

Table 7 List of study interventions for Phase 2

Study groups	*Study interventions**	CCI [redacted]
Flu mRNA_Ph2_1_YA	*F2F23D/DL001Z-NH*	
Flu mRNA_Ph2_2_YA	*F2F23A/DL001Z-NH*	
Flu mRNA_Ph2_3_YA	*F2F23B/DL001Z-NH*	
Control_Ph2_YA	CCI [redacted]	*Refer to Table 9 for details*
Flu mRNA_Ph2_1_OA	*F2F23A/DL001Z-NH*	CCI [redacted]
Flu mRNA_Ph2_2_OA	*F2F23B/DL001Z-NH*	
Flu mRNA_Ph2_3_OA	*F2F23C/DL001Z-NH*	
Control_Ph2_OA	CCI [redacted]	*Refer to Table 9 for details*

CCI [redacted]

YA: younger adult; OA: older adult.

* ***Strains used to design study interventions are based on WHO recommendation for influenza virus vaccine composition for the 2023-2024 NH season.***

CCI [redacted] *: GSKVx000000048110;*** CCI [redacted] ***: GSKVx000000040033;*** CCI [redacted] ***GSKVx000000034794;*** CCI [redacted] ***: GSKVx000000034795;*** CCI [redacted] ***GSKVx000000048111;*** CCI [redacted] ***: GSKVx000000034797;*** CCI [redacted] ***: GSKVx000000034798;*** CCI [redacted] ***GSKVx000000039711.*** Refer to Section 4.3.2 for additional information and Section 6.1 for details on study interventions.

Note: CCI [redacted] .

- Study interventions in Phase 2 will be provided to the site staff/pharmacist in vials containing the CCI [redacted], that will be reconstituted with diluent according to the instructions detailed in Pharmacy Manual, prior to dosing the participants.

Study extension

Participants who complete the Phase 2 part of the study will be offered an opportunity to participate in the extension study (FLU SV MRNA-019).

4.2. Scientific rationale for study design

The study objective is to generate Phase 1/2 reactogenicity, safety, immunogenicity, and dose-finding/dose-confirming data of an mRNA-based CCI [redacted] seasonal influenza vaccine candidate in healthy YA and OAs CCI [redacted]

4.2.1. Rationale for study design of Phase 1

Phase 1 will assess the reactogenicity, safety and immunogenicity of 12 different formulations and 1 active control to CCI [redacted]

The specific aims for Phase 1 (in YAs only) are:

CCI [redacted]

To minimize the number of study groups and number of healthy participants exposed to suboptimal investigational study intervention formulations, the aims of Phase 1 will be investigated using both CCI [redacted] In addition to addressing the specific aims above, this design will CCI [redacted]

CCI [redacted]

The Phase 1 part will be conducted in YAs only as the pattern (in contrast to the magnitude) of immune responses against subtype A and B lineage strains observed in CCI [redacted] was comparable between YAs and OAs (refer to IB for details). The findings in Phase 1 for YAs will therefore be applied to both YA and OA groups in Phase 2.

In Phase 1, all study groups will be enrolled in parallel. Given the careful dose escalation conducted in the FLU SV MRNA-003 (217895) and CV2 SARS-COV2-012 BST (***218595***) studies and the total dose in all study groups will remain below the maximum tolerated dose identified in these studies (refer to Section 4.3.1 for details on dose justification in Phase 1), employing parallel enrolment is considered appropriate.

Comprehensive safety monitoring will be carried out to ensure the safety and wellbeing of the participants (refer to Section 8.3.7 for details). The safety monitoring in Phase 1 includes, but not limited to (1) screening visit, (2) safety laboratory assessment at screening, Day 1, Day 8 and Day 29, (3) inclusion of sentinel participants and review of safety data prior to dosing non-sentinel participants, (4) per site, an interval of at least 60 minutes between dosing of sentinel participants, (5) all participants will be observed on site for a minimum of 60 minutes after dosing, (6) study holding rules, (7) per site, limitation of maximum number of participants dosed per day, (8) across sites, limitation of maximum number of sentinel participants dosed per day and (9) unblinded review of safety data by ***SRT***.

4.2.2. Rationale for study design of Phase 2

Phase 2 will assess the reactogenicity, safety and immunogenicity of 3 different CCI [redacted]. Given the high unmet need for an improved vaccine in OAs, the Phase 2 part will be conducted in both YAs and OAs to confirm that the selected formulation(s) induces an appropriate immune response in both age groups.

All YA and OA study groups are planned to be enrolled in parallel. Given the

a. Safety and reactogenicity data from YAs in the Phase 1 part CCI [redacted], ***and***

b. Safety and reactogenicity data in YA and OA from the FLU SV MRNA-003 (217895) and (CV2 SARS-COV2-012 BST [***218595***]) studies, ***and***

c. Total dose in all study groups will remain below the maximum dose ***evaluated*** in ***Phase 1*** CCI [redacted]***)***, and

d. mRNA-based vaccines are less reactogenic in OAs than in YAs supported by both internal (FLU SV MRNA-003 [217895] and CV2 SARS-COV2-012 BST [***218595***]) and external studies for COVID-19 [Baden, 2021; Polack, 2020] and influenza [Moderna, 2021], employing parallel enrollment and including OAs are considered

appropriate. Refer to IB for details for the safety and reactogenicity data and the maximum tolerated dose.

To ensure the safety and wellbeing of the participants, comprehensive safety monitoring will be carried out (refer to Section 8.3.7 for details). The safety monitoring includes, but not limited to (1) all participants will be observed on site after dosing (for a minimum of 60 minutes for OAs and 30 minutes for YAs), (2) inclusion of sentinel participants in OA groups and review of safety data prior to dosing non-sentinel participants, (3) study holding rules, (4) per site, limitation of maximum number of participants dosed per day in OA groups, (5) across sites, limitation of maximum number of sentinel participants dosed per day in OA groups and (6) review of safety data by ***SRT*** (blinded) and iSRC (unblinded).

Screening visit and safety laboratory assessment will not be included in the Phase 2 part given the accumulation of safety data from the Phase 1 part of the study (312 participants planned to be enrolled) and from the FLU SV MRNA-003 (217895) and CV2 SARS-COV2-012 BST (***218595***) studies.

4.2.3. Rationale for choice of study population and choice of comparator

In this study, participants will be enrolled according to the following age categories:

- Phase 1: 18 to 50 years of age (YAs)
- Phase 2: 18-64 (YA) and 65-85 years of age (OA).

In Phase 1, the target population in the YA groups will be limited to 18 to 50 years of age. In Phase 2, the target population in the YA groups will be 18 to 64 years of age and 65 to 85 years of age in the OA groups. This design will facilitate the generation of additional safety data of the platform CCI [redacted] in a restricted age range prior to expansion to the full target age range for the vaccine candidate. The division of YAs and OAs at 65 years of age is in alignment with the definitions from WHO and CDC [WHO, 2018; CDC, 2022] and several licensed influenza vaccines.

The comparator in Phase 1 is a licensed influenza vaccine approved for use in persons 18 years of age or older. CCI [redacted]. Refer to Section 6.1 for the details on comparator.

4.3. Justification for dose

For all dose levels in Phase 1, the total dose will remain below the maximum tolerated dose identified CCI [redacted] based on the results of the FLU SV MRNA-003 CCI [redacted] and CV2 SARS-COV2-012 BST CCI [redacted] studies using the same mRNA backbone and modified nucleotides (Refer to Section 2.1 and IB for details).

For all dose levels in Phase 2, the total dose will remain below the maximum dose evaluated in YAs in the Phase 1 part CCI [redacted] ***(Refer to IB for details).***

4.3.1. Dose selection for Phase 1

The individual dose level of the mRNAs encoding CCI [redacted] is based primarily on the immunogenicity data from the FLU SV MRNA-003 (217895) study and secondarily on the CCI [redacted] study.

Specifically, CCI [redacted] was selected for comparison based on the findings in FLU SV MRNA-003 (217895) where this dose level induced a superior immune response compared to the active control.

The dose range CCI [redacted] was selected based on the findings in FLU SV MRNA-003 (217895) and CCI [redacted]

For mRNAs encoding CCI [redacted] only data from CCI [redacted] is available which indicated that NA antigens may need relatively CCI [redacted]. However, as the relevance of data generated with CCI [redacted] is not completely clear a CCI [redacted] was selected to provide a sufficiently broad dose range for these antigens.

Refer to Section 2.1 and IB for details on the FLU SV MRNA-003 (217895) and CCI [redacted] studies.

4.3.2. Dose selection for Phase 2

The individual dose level of the mRNAs encoding CCI [redacted] ***are based primarily on the immunogenicity and safety data from the Phase 1 part of this study and secondarily on the FLU SV MRNA-003 (217895) study.***

YA dose selection:

The lowest total dose level evaluated in CCI [redacted] ***) was selected as the maximum dose level for the Phase 2 part in YAs as:***

CCI [redacted]

CCI [redacted]

Considering that a CCI [redacted] ***as compared to the active control,*** CCI [redacted] ***for the Phase 2 part. The*** CCI [redacted] ***were selected as:***

CCI [redacted]

OA dose selection:

The CCI [redacted] ***was selected as the highest dose level for the Phase 2 part in OAs as:***

- ***mRNA-based vaccines are less immunogenic and reactogenic in OAs than in YAs, as supported by both internal (FLU SV MRNA-003 [217895] and CV2 SARS-COV2-012 BST [218595]) and external studies for COVID-19 [Baden, 2021; Polack, 2020] and influenza [Moderna, 2021], and***
- ***No safety signal has been observed in (i) the Phase 1 part of this study*** CCI [redacted] ***and***
- ***A dose level*** CCI [redacted]
- ***Dose levels in the Phase 1 part of this study in YA*** CCI [redacted] ***immune responses in OAs.***

The YA dose levels CCI [redacted] ***with an optimal immunogenicity/reactogenicity profile in OAs. Further, the lowest dose selected in OAs*** CCI [redacted]

Refer to the IB for details on the results from the Phase 1 part of this study as well as from the FLU SV MRNA-003 (217895) and CV2 SARS-COV2-012 BST (218595) studies.

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.

End of Study (EoS) is defined as: LSLV (Visit 6 in Phase 2 part) or Date of the last testing/reading released of the Human Biological Samples, related to primary and secondary endpoints, whichever occurs later. EoS must be achieved no later than 8 months after LSLV. EoS cannot be before 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:

1. A male or female between and including 18 and 50 years of age in Phase 1 and between and including 18 and 85 years of age (YA: 18-64; OA: 65-85) in Phase 2 at the time of the study intervention administration.

2. Healthy participants or medically stable patients as established by medical history, clinical examination and safety laboratory assessments. 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.

3. Body mass index (BMI) $\geq$18 kg/m^2 and $\leq$35kg/m^2.

4. Participants who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g., completion of the eDiary, return for follow up visits).

5. Written informed consent obtained from the participant prior to performing any study-specific procedure.

6. Female participants of non-childbearing potential may be enrolled in the study. Refer to Section 10.4.1.2 for the definition of women of non-childbearing potential.

7. Female participants of childbearing potential may be enrolled in the study if the participant:
   - has practiced adequate contraception for 28 days prior to study intervention administration, and
   - has a negative pregnancy test on the day of study intervention administration, and
   - has agreed to continue adequate contraception for at least 1 month after study intervention administration. Refer to Section 10.4 for the definition of women of childbearing potential 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

1. Only in **Phase 1:** Any clinically significant* hematological, biochemical, urinalysis or HbA1c laboratory abnormality.

   **The investigator should use his/her clinical judgment to decide which abnormalities are clinically significant.*
2. Participant tested positive for influenza by local health authority-approved testing methods within 180 days prior to Day 1.
3. Current or past malignancy, unless completely resolved without clinically significant sequelae (e.g., scars following surgical resection for treatment of basal cell carcinoma cases are allowed) for >5 years.
4. Any confirmed or suspected immunosuppressive or immunodeficient condition, including HIV infection, based on medical history and physical examination (no laboratory testing required). However, in **Phase 2,** 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/mm³ and their viral load has been undetectable (i.e., HIV-RNA <50 copies/mL) (based on medical records, no laboratory testing required). ***For country specific instruction please refer to Section 10.6.***
5. History of myocarditis or pericarditis less than or equal to 10 years prior to vaccine administration, including a history of myocarditis or pericarditis following vaccination with an mRNA COVID-19 vaccine.
6. Participants with history of hypersensitivity or severe allergic reaction to any previous vaccine or hypersensitivity likely to be exacerbated by any component of the study intervention (including latex, polyethylene glycol, egg protein and aminoglycoside antibiotics).
7. History of, or uncontrolled neurological disorders or seizures, including Guillain-Barré syndrome and Bell's palsy, with the exception of febrile seizures during childhood.

8. Any history of dementia or any medical condition that moderately or severely impairs cognition.
9. Any medical condition that in the judgment of the investigator would make intramuscular injection unsafe.
10. Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the participant due to participation in the study.

5.2.2. Prior/Concomitant therapy

11. Administration of an influenza vaccine (including any of the study investigational vaccines) within 180 days before enrollment or planned administration within 28 days (Day 29) after the study intervention administration.
12. ***Phase 1:*** Administration of a vaccine not foreseen by the study protocol in the period starting 28 days (Day -28) before the study intervention administration, or planned administration within 28 days (Day 29) after the study intervention administration*. ***Phase 2: Administration of a vaccine not foreseen by the study protocol in the period starting 15 days (Day -15) before the study intervention administration, or planned administration within 28 days (Day 29) after the study intervention administration*.***

    **In case 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 to 7 days if, necessary for that vaccine, provided it is used according to the local governmental recommendations and that the Sponsor is notified accordingly*.
13. 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.
14. Administration of long-acting immune-modifying drugs within 90 days before enrollment or planned use at any time during the study period (e.g., infliximab).
15. 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. Administration of monoclonal antibodies specifically directed against the spike protein of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), for treatment of COVID-19 disease is allowed.
16. Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting 3 months prior to the study intervention administration. For corticosteroids, this will mean prednisone equivalent ≥20 mg/day. Inhaled, topical and intraarticular steroids are allowed.

5.2.3. Other exclusions

17. 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).
18. Pregnant or lactating female.
19. Bedridden participants.
20. Female planning to become pregnant or planning to discontinue contraceptive precautions within the 1-month post-dosing period.
21. Alcoholism or substance use disorder within the past 24 months based on the presence of 2 or more of the following abuse criteria: hazardous use, social/interpersonal problems related to use, neglect of major roles to use, withdrawal, tolerance, use of larger amounts or longer, repeated attempts to quit or control use, much time spent using, physical or psychological problems related to use, activities given up to use, craving.
22. Any study personnel or their immediate dependents, family, or household members.
23. Participants with extensive tattoos covering deltoid region on both arms that would preclude the assessment of local reactogenicity.

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 Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes informed consent date, demography, screen failure details and eligibility criteria.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned the same participant number if they are rescreened within the screening period (Day -28 Day -1).

5.5. Criteria for temporarily delaying enrollment/randomization/administration of study intervention

Study intervention administration may be postponed within the permitted time interval (Table 3) 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.
- Use of antipyretics and/or analgesics within 24 hours prior to study intervention administration, with exception of use of low dose of acetyl salicylic acid for prevention of cardiovascular disease.
- Close contact in the past 14 days prior to Visit 1 (Day 1) with at least 1 person diagnosed with SARS-COV-2 (laboratory-confirmed or a clinical diagnosis). Close contact is defined as standing less than 2 meters or 6 feet away from an infected person for a cumulative total of 15 minutes or more over a 24-hour period. Dosing will be delayed until 14 days after the last contact, unless the participant has tested negative for SARS-COV-2 in the meantime.
- Close contact with persons with influenza (clinical diagnosis) in the past 14 days prior to Visit 1. Close contact is defined as standing less than 2 meters or 6 feet away from an infected person for a cumulative total of 15 minutes or more over a 24-hour period. Dosing will be delayed until 14 days after the last contact, unless the participant has tested negative for flu in the meantime.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

The definition of study intervention is provided in the table of definitions.

6.1. Study intervention(s) administered

Study interventions in Phase 1 listed in Table 8 will be manufactured as separate components (investigational medicinal products [IMPs]) that will be provided to the site staff/pharmacist, who will be responsible to combine them at according to the scheme provided in the Table 6 before dosing each participant.

Study interventions in Phase 2 will be provided to the site staff/pharmacist in vials containing CCI [redacted], that will be reconstituted with diluent according to the instructions detailed in Pharmacy Manual, prior to dosing the participants.

Table 8 Study intervention(s) administered. Phase 1 - (Table spreading through multiple pages)

Study intervention name:	Flu Seasonal mRNA *
Study intervention formulation:	CCI [redacted]

Study intervention name:	**Flu Seasonal mRNA ***							
Presentation:	CCI [redacted]							
Manufacturer:	GSK Biologicals	BBRAUN**	GSK Biologicals	BBRAUN**	GSK Biologicals	BBRAUN**	GSK Biologicals	BBRAUN**
Type:	Investigational							
Product category:	Biologic							
Route of administration:	IM							
Location	Deltoid							
Directionality	Upper							
Laterality ***	Non-Dominant							
Number of doses to be administered:	1							
Volume to be administered by dose:	Refer to the Pharmacy Manual							
Packaging and labeling:	Refer to the Pharmacy Manual for more details							

Study intervention name:	**Flu Seasonal mRNA***			
Study intervention formulation:	CCI [redacted]			
Presentation:	CCI [redacted]			
Manufacturer:	GSK Biologicals	BBRAUN**	GSK Biologicals	BBRAUN**
Type:	Investigational			
Product category:	Biologic			
Volume to be administered by dose:	Refer to the Pharmacy Manual			
Route of administration:	IM			
Location	Deltoid			
Directionality	Upper			
Laterality *	Non-Dominant			
CCI [redacted]				
Packaging and labeling:	Refer to the Pharmacy Manual for more details			

Study intervention name:	Flu Seasonal mRNA *					
Study intervention formulation:	CCI	Excipients; Water for injections	CCI	Excipients; Water for injections	CCI	Excipients; Water for injections

Study intervention name:	**Flu Seasonal mRNA ***					
Presentation:	CCI [redacted]					
Manufacturer:	GSK Biologicals	BBRAUN**	GSK Biologicals	BBRAUN**	GSK Biologicals	BBRAUN**
Type:	Investigational					
Product category:	Biologic					
Number of doses to be administered:	CCI [redacted]					
Volume to be administered by dose:	Refer to the Pharmacy Manual					
Route of administration:	IM					
Location	Deltoid					
Directionality	Upper					
Laterality ***	Non-Dominant					
Packaging and labeling:	Refer to the Pharmacy Manual for more details					

Study intervention name:	**Flu Seasonal mRNA ***
	CCI [redacted] CCI
Study intervention formulation:	[redacted]

Study intervention name:	**Flu Seasonal mRNA ***						CCI [redacted]
	CCI [redacted]						
Presentation:	CCI [redacted]						
Manufacturer:	GSK Biologicals	BBRAUN**	GSK Biologicals	BBRAUN**	GSK Biologicals	BBRAUN**	GSK Biologicals
Type:	Investigational						Active control
Product category:	Biologic						CCI [redacted]
Number of doses to be administered:	CCI [redacted]						
Volume to be administered by dose:	Refer to the Pharmacy Manual						

Study intervention name:	**Flu Seasonal mRNA ***	CCI [redacted]
	CCI [redacted]	
Route of administration:	IM	
Location	Deltoid	
Directionality	Upper	
Laterality ***	Non-Dominant	
Packaging and labeling:	Refer to the Pharmacy Manual for more details	

* Strains used to design study interventions are based on WHO recommendation for influenza virus vaccine composition CCI [redacted].
** Another manufacturer might be used depending on study site.
*** 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.

Table 9 Study intervention(s) administered. Phase 2

Study intervention name:	Younger adults			
	Flu Seasonal mRNA*			CCI [redacted]
Study intervention formulation:	CCI [redacted]			CCI [redacted]

Study intervention name:	**Younger adults**						
	Flu Seasonal mRNA*						CCI
Presentation:	CCI						CCI
Manufacturer:	GSK Biologicals	BBRAUN**	GSK Biologicals	BBRAUN**	GSK Biologicals	BBRAUN**	GSK Biologicals
Type:	Investigational						Active control
Product category:	Biologic						CCI
Volume to be administered by dose:	Refer to the Pharmacy Manual						
Route of administration:	IM						
Location	Deltoid						
Directionality	Upper						
Laterality ***	Non-Dominant						
Number of doses to be administered:	CCI						
Packaging and labeling:	Refer to the Pharmacy Manual for more details						

Study intervention name:	**Older adults**	
	Flu Seasonal mRNA*	CCI [redacted]
Study intervention formulation:	CCI [redacted]	CCI [redacted]

Study intervention name:	**Older adults**						
	Flu Seasonal mRNA*						CCI
	CCI						
Presentation:							CCI
Manufacturer:	GSK Biologicals	BBRAUN**	GSK Biologicals	BBRAUN**	GSK Biologicals	BBRAUN**	Sanofi Pasteur
Type:	Investigational						Active control
Product category:	Biologic						Combination product
Volume to be administered by dose:	Refer to the Pharmacy Manual						0.7 mL
Route of administration:	IM						
Location	Deltoid						
Directionality	Upper						
Laterality ***	Non-Dominant						
Number of doses to be administered:	CCI						
Packaging and labeling:	Refer to the Pharmacy Manual for more details						

CCI [redacted].

* Strains used to design study interventions will be based on WHO recommendation for influenza virus vaccine composition CCI [redacted].

** Another manufacturer might be used depending on study site.

*** 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.

CCI [redacted].

All the participants in Phase 1, must be observed closely for at least 60 minutes after the administration of the study intervention. All OA participants in Phase 2 will be observed on site for a minimum of 60 minutes after dosing. All YA participants in Phase 2 must be observed closely for at least 30 minutes after dosing for detection of immediate allergic reactions [Shimabukuro, 2021].

Appropriate resuscitation equipment, medical treatment and trained staff must be readily available during the observation period in case of anaphylaxis, syncope.

6.1.1. Medical devices

- Licensed vaccines used as active controls in this study are provided as a single-dose pre-filled syringe (i.e., considered as combination product).
- Other medical devices (e.g., syringes, thermometers) may be provided for use in this study. Refer to the study Pharmacy Manual for instructions on use of medical devices.
- All device deficiencies (including malfunction, use error and inadequate labeling) shall be documented and reported by the investigator throughout the clinical investigation (see Sections 8.4.7 and 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

All participants will be centrally assigned to randomized study intervention using an automated Internet-based system, Source data Base for Internet Randomization (e.g., SBIR). Before the study is initiated, the log-in information and directions for SBIR will be provided to each site.

Participant identification numbers will be assigned sequentially to the participants who have consented to participate in the study, according to the range of participant identification numbers allocated to each study center. Additionally, a QR code will be generated for each participant to allow faster identification and management of biological samples. This QR code will be linked to participant's identification number and will not contain any other participant-related information.

Once a participant identification number is allocated, the randomization system will determine study group and will provide the study intervention number to be used.

When SBIR is not available, please refer to the SBIR user guide for specific instructions.

In Phase 1 of the study, the randomization algorithm will use a minimization procedure accounting for sentinel status as a stratification factor, and study, country, center, and flu vaccination history during past 2 years as minimization factors.

For Phase 2, the randomization algorithm will use a minimization procedure accounting for age group and sentinel status as a stratification factors, and study, country, center, and flu vaccination history during past 2 years as minimization factors. In addition, an exploratory immunogenicity subset consisting of ***approximately 50*** participants in each group will be defined CCI [redacted]. This subset will be enrolled in dedicated centers.

The randomization of supplies within blocks will be performed at GSK, using MATerial Excellence (MatEx), a program developed for use in Statistical Analysis System (SAS) (Cary, NC, US) by GSK. Entire blocks will be shipped to the study centers/warehouse(s).

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

6.4. Blinding

This study will be single-blind for Phase 1 and observer-blind for Phase 2. Refer to Definitions Of Terms for definition of single-blind and 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. For Phase 1, to limit the testing of samples to relevant assays, the laboratory may be provided with list of participant codes to be considered CCI [redacted]

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 regulatory 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

SBIR will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. 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 SBIR, 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 investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents.

6.6. Dose modification

This Section is not applicable.

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

This Section is not applicable.

6.8. Treatment of overdose and management of anaphylaxis

An overdose is any dose of study intervention given to a participant that exceeds the planned, randomized dose for an individual within a given dose group.

GSK does not recommend specific treatment for an overdose.

The appropriate medical treatment to be administered for any episode of anaphylaxis or other immediate AEs, including those associated with overdose, will be based on the judgment of the medical team/physician attending to the participant.

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, except vitamins and dietary supplements, administered after the study intervention administration (Day 1) until Day 28.
- All concomitant medication leading to withdrawal from Day1 to Day 183. Refer to Section 5.2.2 for more information.
- Any concomitant vaccination administered in the period starting 28 days before study intervention administration (Day -28) until Day 28.
- Administration of any influenza vaccine 2 years prior to dosing and up to Day 183.
- All concomitant medication which may explain/cause/be used to treat an SAE/AESI including vaccines/products, as defined in Sections 8.4.1 and 10.3.5. These must also be recorded in the Expedited Adverse Event report.
- All concomitant medications associated with medically attended events (MAEs), including vaccines/products, except vitamins and dietary supplements, administered after the study intervention administration (Day 1) until the last visit (Day 183).
- Prophylactic medication (i.e., medication administered in the absence of any symptom and in anticipation of a reaction to the vaccination).

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:

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

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

Refer to Section 5.2.2 for the details on exclusionary concomitant medication for this study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of study intervention

This Section is not applicable.

7.2. Participant discontinuation/withdrawal from the 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.

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

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

All data and samples collected up to and including the date of withdrawal of/last contact with the participant will be included in the study analyses. 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 requiring reporting to GSK
- Unsolicited non-serious AE
- Solicited AE
- Lost to follow up
- Physician decision
- 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 10.3.5.6).

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:

1. 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.
2. 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.
3. Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

1. Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
2. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
3. 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'.
4. 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.
5. Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

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, transcribing responses to eDiaries, 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 (screening visit in Phase 1 part or Visit 1 in Phase 2 part) 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 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 and flu vaccination history for the past 2 years 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 the screening visit (in Phase 1 only) or to Visit 1 (Day 1 in Phase 1 and Phase 2). 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 download the eDiary application on his/her own electronic device. For 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 his/her health post-dosing (e.g., solicited events, responses to the [redacted] The study staff will train the participant on the use of the eDiary and emphasize the importance of completing the eDiary throughout the eDiary data collection period.

The study staff will train the participant and/or his/her caregiver (if identified by the study participant) on the use of the eDiary.

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 for research not planned in this protocol. In this case, all participants in countries where this is allowed will be asked to give consent to allow GSK or a contracted partner, to use the samples for further research. The further research will be subject to prior IEC/IRB approval, if required by local legislation.

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

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

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

8.2.1. Biological samples

Approximate amount of blood collected from each participant, over the duration of the study, is summarized in the SoA (Section 1.3) and Table 10.

Table 10 Approximate volume of blood collected at each time point and during the whole study

	Sample type	Day -28 to Day 1	Day 1	Day 2	Day 8	Day 29	Day 92	Day 183	Total
Phase 1	Blood	10 mL	40 mL	-	10 mL	40 mL	30 mL*	30 mL*	160 mL
Phase 1	Urine**	As per local practice							
Phase 2 (YA and OA subset participants***)	Blood	-	79 mL	5 mL	69 mL	30 mL	10 mL*	70 mL*	263 mL
Phase 2 (non-subset YA participants)	Blood	-	30 mL†	-	-	30 mL†	30 mL*, †	30 mL *, †	120 mL
Phase 2 (non-subset OA participants)	Blood	-	10 mL	-	-	10 mL	10 mL*	10 mL*	40 mL

* Blood samples should only be collected for participants who did not receive a standard of care vaccination against seasonal flu since their enrollment into the study.
** Urine sample will only be taken for screening purposes in Phase 1.
*** Refer to Section 6.3 for subset description.
† Part of the blood samples might be used for assay development and validation.

8.2.2. Laboratory assays

Table 11 Laboratory assays

Test classification	System	Component	Challenge	Method	Laboratory*
Humoral immunity (Antibody determination)	Serum	CCI		CCI	GSK or GSK designated lab
	Serum				GSK or GSK designated lab
	Serum				GSK or GSK designated lab
	Serum				GSK or GSK designated lab
	Serum				GSK or GSK designated lab
	Serum				GSK or GSK designated lab

Test classification	System	Component	Challenge	Method	Laboratory*
	Serum	CCI		CCI	GSK or GSK designated lab
	Serum				GSK or GSK designated lab
	Serum				GSK or GSK designated lab
CCI			CCI		GSK or GSK designated lab
					GSK or GSK designated lab
	Whole blood (CCI				GSK or GSK designated lab
Innate immunity	Plasma		N/A		GSK or GSK designated lab

Ab: antibody; CCI ; MN: microneutralization CCI CCI ; N/A: not applicable; CCI .
* Refer to the list of clinical laboratories for details.
** CCI
† Only when possible.

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 (such as, but not limited to, CCI might be done during or after the study if deemed necessary 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 12 Immunological read-outs

Blood sampling timepoint		Subset name	*Approximate* No. *of* participants	Component
Type of contact and timepoint	Sampling timepoint			
Day 1	Pre-dose	All enrolled participants (Phase 1 and Phase 2)	***1272***	CCI [redacted]
		Participants in exploratory immunogenicity subset (Phase 2)	***400***	
			For CCI [redacted] sample collection will be limited to selected sites.	
			400	
			400	
			400	
			400	
Day 2	Post-dose	Participants in exploratory immunogenicity subset (Phase 2)	***400***	
Day 8	Post-dose	Participants in exploratory immunogenicity subset (Phase 2)	***400***	
			For CCI [redacted] sample collection will be limited to selected sites.	
			400	
			400	
Day 29	Post-dose	All enrolled participants (Phase 1 and Phase 2)	***1272***	
		Participants in exploratory immunogenicity subset (Phase 2)	***400***	
			400	
Day 92	Post-dose	All enrolled participants (Phase 1 and Phase 2)	***1272***‡	

Blood sampling timepoint		Subset name	*Approximate* No. *of* participants	Component
Type of contact and timepoint	**Sampling timepoint**			
Day 183	Post-dose	All participants enrolled (Phase 1 and Phase 2)	***1272***‡	CCI [redacted]
		Participants in exploratory immunogenicity subset (Phase 2)	***400***‡	
			400‡	
			400‡	
			400‡	

Ab: antibody; CCI [redacted]
* Strains used to design the study intervention
** CCI [redacted]
‡ Given that samples will only be collected from participants who did not receive a standard of care vaccination against seasonal flu, this number represents the maximum number of participants who will have a sample collected for the Visit.

8.2.4. Immunological correlates of protection

CCI [redacted]

8.3. Safety assessments

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

8.3.1. Physical examination

1. During the screening visit (in Phase 1 only) and prior to dosing 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 10 minutes of rest, body weight and height. Vital signs are to be taken before blood collection for laboratory tests.
2. If the investigator determines that the participant's health on the day of study intervention administration temporarily precludes dosing, the visit will be rescheduled. Refer to the Section 5.5 for the list of criteria for temporary delay of study intervention administration.
3. If the participant reported any pre-existing medical condition, the investigator would extend the physical examination according to his/her medical judgment to ensure that the participant meets all the inclusion/exclusion criteria.

4. Treatment of any abnormality observed during physical examination must be performed according to local medical practice outside this study or by referral to an appropriate health care provider.
5. Physical examination at each study visit after the dosing visit, 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.

8.3.2. Pre-dosing body temperature

The body temperature of each participant needs to be measured prior to the study vaccine 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 dosing, as specified in SoA (Section 1.3).

Refer to the approved product label/package insert.

8.3.4. Myocarditis and pericarditis assessment and definitions

All potential cases of myocarditis or pericarditis will undergo diagnostic work-up and be clinically evaluated.

To detect asymptomatic participants, cardiac troponin (Troponin I and/or Troponin T) testing will be performed for all study participants on Day 1, Day 8 and Day 29 in Phase 1 of the study. An abnormal cardiac troponin test on Day 8 or Day 29 will be repeated for confirmation.

Cardiac symptoms of myocarditis and/or pericarditis include the following: acute chest pain or pressure; palpitations; dyspnea after exercise, at rest or lying down; and diaphoresis. Non-specific symptoms may include fatigue, abdominal pain, dizziness or syncope, edema, cough, ***cyanosis, weakness, shoulder and/or upper back pain, nausea, vomiting, diarrhea, altered mental status and low-grade intermittent fever*** [SPEAC, 2022].

Phase 1: The following cases will be referred to a cardiologist or emergency room (as appropriate) for further evaluation and management following current practice guidelines (e.g., American Heart Association or local standard of care):

- Asymptomatic participants with elevated cardiac troponin values on Day 8 or Day 29 (confirmed on repeat testing) following a normal cardiac troponin value at baseline (Day 1), with no other identifiable cause of the finding.

- Symptomatic participants with ≥1 new or worsening cardiac symptom or ≥2 new or worsening non-specific symptoms within 4 weeks after dosing, with no potential alternative etiology, as assessed by the investigator [SPEAC, 2022].

Phase 2: Monitoring for asymptomatic participants by routine screening for elevated cardiac troponin will not be included in the Phase 2 part of the study. However, an expanded focus on symptom identification (including participant specific educational material), unscheduled study site visits for further evaluation, and an extended monitoring time period will be implemented as outlined below.

- ***Participants will be provided with educational materials, as part of the consent process, describing the signs and symptoms of myocarditis and pericarditis as well as guidance on how and when to seek medical care and contacting study personal.***
- ***If the participant develops ≥1 new or worsening cardiac symptoms, and/or ≥2 new or worsening non-specific symptoms within 6 weeks after dosing with no potential alternative etiology, as assessed by the Investigator, an unscheduled study site visit will take place immediately (or an emergency room visit as per clinical judgment by the investigator) where a full physical examination, an ECG (if a study site does not have the capability to conduct an ECG, an alternative medical facility/ qualified vendor can be used), screening of a cardiac biomarker (Troponin I and/or Troponin T), and screening of an inflammatory marker (CRP, erythrocyte sedimentation rate or D-dimer) will be done.***
- ***If the ECG, the cardiac biomarker and/or the inflammatory marker results are abnormal with no potential alternative etiology, as assessed by the investigator, the participant will be referred to a cardiologist immediately (or an emergency room visit as per clinical judgment by the investigator) for further evaluation and management following current practice guidelines (e.g., American Heart Association or local standard of care).***

Definitive, probable and possible cases of myocarditis/pericarditis (per Brighton case definitions [SPEAC, 2022]) will be determined by the cardiologist and reported as an AESI. Participants will be followed-up until cardiac evaluation is completed, and/or symptoms have resolved, whichever comes later.

Definitive, probable and possible cases of myocarditis or pericarditis occurring in temporal association with vaccination of study participants will be submitted as expedited reports following suspected unexpected serious adverse reaction (SUSAR) reporting timelines.

8.3.5. Clinical safety laboratory tests

- See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3).
- The investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents.

- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
  - In the absence of a diagnosis, abnormal laboratory findings assessments or other abnormal results the investigator considers clinically significant will be recorded as an AE or SAE, if they meet the definition of an AE or SAE (refer to Sections 10.3.1 and 10.3.2).
  - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
  - If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE), then the results must be recorded.

8.3.6. Pregnancy testing

- For women of childbearing potential: only women with negative pregnancy test result at the screening visit (in Phase 1) and at Visit 1 (in Phase 1 and Phase 2) will be included in the study. The study intervention may only be administered if the pregnancy test result is negative at Visit 1 (Day 1, both in Phase 1 and 2). Refer to Section 10.4.1.1 for definition of women of childbearing potential.
- Female participants of childbearing potential must perform a urine pregnancy test before the administration of any dose of study intervention. If time allows, serum pregnancy test can be done as per local requirements. 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.
- Refer to Section 8.4.6 for the information on study continuation for participants who become pregnant during the study.

8.3.7. Study holding rules, safety monitoring committee

8.3.7.1. Safety monitoring

Participant safety will be continuously monitored by the medical monitor, designated Safety Lead (or delegate) and ***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 ***SRT*** will oversee the unblinded safety monitoring in Phase 1 and blinded safety monitoring in Phase 2 whereas the iSRC will oversee the unblinded safety monitoring in Phase 2. Refer to Section 10.1.6 for the ***SRT*** and iSRC composition and role.

Safety monitoring for Phase 1 and Phase 2 participants is specified in SoA (Section 1.3), Figure 1 and Figure 2, and the safety endpoints are presented in Section 3.

Safety assessments for Phase 1 and Phase 2 participants are listed in Section 8.3. Study holding rules are listed in Section 8.3.7.1.2. Additional safety assessments for Phase 1 participants are listed in Section 10.2.

8.3.7.1.1. Phase 1

Early participants in each group in Phase 1 will be referred to as 'sentinel participants'. Enrollment and dosing of sentinel and non-sentinel participants will be managed as described below.

- Sentinel participants will be the first 5 participants to be enrolled and dosed in each group.
- On a per site level, sentinel participants will be dosed with an interval of at least 60 minutes between them. On a per site level, a maximum of 7 sentinel participants will be dosed per day and across sites, a maximum of 20 sentinel participants will be dosed per day. All sentinel participants will be observed on site for a minimum of 60 minutes after dosing.
- A safety follow up contact (Contact 1) for all sentinel participants will be performed approximately 20 hours post-dosing.
- After at least 7 days (Day 8) of follow up of sentinel participants, a ***SRT*** meeting will occur where all available safety data will be reviewed. The ***SRT*** will decide for each group whether to allow the dosing of non-sentinel participants. The investigator is not permitted to start dosing the non-sentinel participants prior to receipt of the ***SRT*** meeting outcome. However, screening procedures for non-sentinel participants may be performed prior to receipt of the ***SRT*** meeting outcome.
- For groups obtaining a favorable decision from the ***SRT***, non-sentinel participants can be dosed (unless a holding rule is met). All participants will be observed on site for a minimum of 60 minutes after dosing.
- On a per site level, a maximum of 15 participants will be dosed per day.
- After at least 28 days (Day 29) of follow up of all participants, a ***SRT*** meeting will occur where all available safety data will be reviewed. The ***SRT*** will evaluate the overall safety profile for each group and provide a summary to the iDRC (refer to Section 4.3.2 for dose selection for Phase 2).
- In addition to the scheduled meetings above, the ***SRT*** will periodically evaluate the safety data as it becomes available, during the enrollment and follow up period.
- If any safety concerns are identified outside of scheduled ***SRT*** meetings, an ad-hoc ***SRT*** meeting will occur, during the enrollment and follow up periods.

Refer to Section 8.3.7.1.2 for Phase 1 holding rules.

8.3.7.1.2. Phase 2 (YA groups)

In Phase 2, enrollment and dosing of YA participants will be performed as described below.

- Participants in all groups can be enrolled and dosed without restrictions (unless a holding rule is met). All participants will be observed on site for a minimum of 30 minutes after dosing.
- The ***SRT*** and iSRC will periodically evaluate the safety data as it becomes available, during enrollment and follow up.
- If any safety concerns are identified outside of scheduled ***SRT*** and iSRC meetings, ad-hoc meetings will occur, during the enrollment and follow up periods.

Refer to Section 8.3.7.2 for Phase 2 holding rules.

8.3.7.1.3. Phase 2 (OA groups)

In Phase 2, enrollment and dosing of OA participants will be performed as described below. Early participants in each group will be referred to as 'sentinel participants'.

- Sentinel participants will be the first 5 participants to be enrolled and dosed in each group.
- On a per site level, sentinel participants will be dosed with an interval of at least 60 minutes between them. On a per site level, a maximum of 7 sentinel participants will be dosed per day and across sites, a maximum of 20 sentinel participants will be dosed per day. All sentinel participants will be observed on site for a minimum of 60 minutes after dosing.
- A safety follow up contact (Contact 1) for all sentinel participants will be performed approximately 20 hours post-dosing.
- After at least 7 days (Day 8) of follow up of sentinel participants, a iSRC meeting will occur where all available safety data will be reviewed. The iSRC will decide for each group whether to allow the dosing of non-sentinel participants. The investigator is not permitted to start dosing the non-sentinel participants prior to receipt of the iSRC meeting outcome.
- For groups obtaining a favorable decision from the iSRC, non-sentinel participants can be dosed (unless a holding rule is met). All non-sentinel participants will be observed on site for a minimum of 60 minutes after dosing.
- On a per site level, a maximum of 15 participants will be dosed per day.
- In addition to the scheduled meeting above, the iSRC will periodically evaluate the safety data as it becomes available, during the enrollment and follow up period.
- If any safety concerns are identified outside of scheduled iSRC meetings, an ad-hoc iSRC meeting will occur, during the enrollment and follow up periods.

Refer to Section 8.3.7.2 for Phase 2 holding rules.

8.3.7.2. Study holding rules

The safety holding rules for Phase 1 and Phase 2, are defined in the Table 13 ***and Table 14, respectively***. Holding rules 1a-f will be assessed by the investigator on a continuous basis. Holding rules 2a and 2b will be assessed by the ***SRT*** in Phase 1 and iSRC in Phase 2 during the safety evaluations of the data. Meeting any of these holding rules will trigger a hold of study intervention administration irrespective of number of participants enrolled and/or timing of the event, for all the study groups.

Of note, no formal holding rules will be applied for other reactogenicity and safety data, such as missed visits due to study intervention-related AEs, Grade 1 and Grade 2 solicited unsolicited AEs in the 7-day follow up period (Day 1 to Day 7) and unsolicited AEs collected from Day 8 to Day 28 after study intervention administration. However, if available, these data will also be reviewed by the ***SRT***/iSRC to allow an overall assessment of the benefit/risk ratio of study intervention administration, for each group.

Table 13 Study holding rules *for Phase 1*

Holding rule	Events, per dose and per individual study group	Number of participants to pause dosing in all groups, pending further evaluation by the *SRT*
1a	Death or any life-threatening **SAE** regardless of causality	≥1
1b	Any non-life-threatening **SAE** that cannot reasonably be attributed to a cause other than study intervention administration as per Investigator or Sponsor assessment	≥1
1c	Any withdrawal from the study (by investigator or participant request) due to a Grade 3 AE that cannot reasonably be attributed to a cause other than study intervention administration	≥1
1d	Necrosis at the injection site	≥1
1e	Confirmed myocarditis or pericarditis events not clearly attributable to any cause other than study vaccine	≥1
1f	Laryngospasm, bronchospasm, or anaphylaxis within 24 hours after administration of study intervention	≥1
2a	Maximum number of participants with the same **Grade 3 solicited local or systemic AE** in an investigational vaccine group, with onset within the 7-day (Day 1-7) post-dosing period	≥2
2b	Maximum number of participants with the **same or similar Grade 3 related unsolicited AE in an investigational vaccine group, including events with an identical MedDRA High Level Term** and events assessed as clinically similar. *Includes any Grade 3 or above laboratory abnormalities* of clinical relevance, symptomatic or not, as determined by the investigator*	≥2

* Grading of laboratory parameters will be based on the FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials". N/A: not applicable

Table 14 Study holding rules for Phase 2

Holding rule	*Events, per dose and per individual study group*	*Number of participants to pause dosing in all groups, pending further evaluation by the iSRC*
1a	*Death or any life-threatening SAE regardless of causality*	*≥1*
1b	*Any non-life-threatening SAE that cannot reasonably be attributed to a cause other than study intervention administration as per Investigator or Sponsor assessment*	*≥1*
1c	*Necrosis at the injection site*	*≥1*
1d	*Confirmed myocarditis or pericarditis events not clearly attributable to any cause other than study vaccine*	*≥1*
1e	*Laryngospasm, bronchospasm, or anaphylaxis within 24 hours after administration of study intervention*	*≥1*
2a	*Maximum number of participants with the same Grade 3 solicited local or systemic AE (same solicited AE lasting 2 consecutive days [48 hours] or more as grade 3)* in an investigational vaccine group, with onset within the 7-day (Day 1-7) post-dosing period*	*≥5% (and ≥2)*
2b	*Maximum number of participants with the same or similar Grade 3 related unsolicited AE in an investigational vaccine group, including events with an identical MedDRA High Level Term and events assessed as clinically similar. Includes any Grade 3*	*≥5% (and ≥2)*

** E.g., 2 cases of grade 3 fever occurring 2 consecutive days in 2 participants in the same group*

Refer to Section 4.3 for details on selection of doses for further assessment for the next phase of the study.

If a holding rule is met, the investigator must suspend administration of the study intervention and inform GSK immediately (e.g., holding rules 1a-f). Refer to Table 18 for contact information.

The following communication sequence must be followed:

- The concerned site staff has to put study intervention administration on hold.
- The concerned site staff must immediately inform their local GSK contact defined in the Table 18.
- GSKs local medical contact will inform the other sites of their country and the study Clinical Lead. GSK will put the randomization in SBIR on hold.
- The study Clinical Lead will ensure that all local medical contacts in all study countries are notified.
- All informed site staff will confirm to their local contact that action has been taken providing appropriate documentation to GSK.
- GSK will further evaluate the case with the ***SRT*** and GSK Global Safety Board and will take the decision to stop or to restart the study intervention administration. All site staff will be informed about that final decision by their local GSK contact.

GSK will inform the investigator if holding rules 2a ***or*** b are met or if a safety signal is observed during the safety evaluation by the ***SRT***/iSRC.

- GSK will put the randomization in SBIR on hold.
- The study Clinical Lead will ensure that all local medical contacts in all study countries are notified upon meeting holding rules 2a-2b.
- Local medical contacts will inform all the sites of their country that a holding rule is met. Following this notification, the study intervention administration should be put on hold.
- All informed site staff will confirm to their local contact that action has been taken providing appropriate documentation to GSK.
- GSK will further evaluate the case with the ***SRT***, iSRC and GSK Global Safety Board and will take the decision to stop or to restart the study intervention administration. All site staff will be informed about that final decision by their local GSK contact.
- In case of favorable outcome of the safety evaluations, randomization in SBIR will be re-launched allowing the investigators to restart enrollment and dosing of the remaining participants in the study.

Refer to ***SRT*** framework, iSRC charter or relevant procedure for details on communication regarding holding rules.

8.4. Adverse events (AEs) serious adverse events (SAEs), 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 AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (see Section 7). 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/or Section 10.5.

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

All SAEs will be collected from the day of study intervention administration (Day 1) until LSLV (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) or related to a GSK product (non-IMP) will be recorded 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 events) at the timepoints specified in the SoA.

Medical occurrences 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 15.

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. If the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

Table 15 Collection and reporting of safety information

Event	Pre-Dose* D-28 to D-1	Dose D1	D7	D28	D183
SAEs assessed as related to study participation** or concurrent GSK medication/ vaccine					
Administration site solicited events					
Systemic solicited events					
Unsolicited AEs					
SAEs					
AESIs					
Pregnancies					
AEs leading to withdrawal from study					
Intercurrent medical conditions***					

Event	Pre-Dose* D-28 to D-1	Dose D1	D7	D28	D183
MAEs****					

D: Day
* i.e., informed consent obtained
** 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.
*** Intercurrent medical conditions are defined as medical conditions that occur after vaccine administration and either preclude observation of the outcome of interest (immunogenicity/efficacy endpoint) or affect its interpretation (by altering the immune response to vaccination or altering the initial immune status of the participant).
**** An AE that results in an unscheduled visit to a medical professional (e.g., physician's office visits, emergency room visits or hospitalization).
The shaded region in the table indicates time period of data collection.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in 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.

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 15.

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, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

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 AEs of special interest (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 Sections 10.3.5.6 and 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 Sections 8.4.1 and 9.2.

8.4.4. AEs of special interest

8.4.4.1. Potential immune-mediated diseases

Potential immune-mediated diseases (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 16.

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 16 List of potential immune-mediated diseases (pIMDs)

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

Medical Concept	Additional Notes
Pulmonary alveolar proteinosis (PAP)	• Frequently used related terms include: “pulmonary alveolar lipoproteinosis”, “phospholipidosis”
Endocrine disorders	
Addison’s disease	
Autoimmune / Immune-mediated thyroiditis	Including but not limited to: • Hashimoto thyroiditis (autoimmune hypothyroidism, lymphocytic thyroiditis) • Atrophic thyroiditis • Silent thyroiditis • Thyrotoxicosis
Autoimmune diseases of the testis and ovary	• Includes autoimmune oophoritis, autoimmune ovarian failure and autoimmune orchitis
Autoimmune hyperlipidemia	
Autoimmune hypophysitis	
Diabetes mellitus type I	
Grave's or Basedow’s disease	• Includes Marine Lenhart syndrome and Graves' ophthalmopathy, also known as thyroid eye disease (TED) or endocrine ophthalmopathy
Insulin autoimmune syndrome	
Polyglandular autoimmune syndrome	• Includes Polyglandular autoimmune syndrome type I, II and III
Eye disorders	
Ocular Autoimmune / Immune-mediated disorders	Including but not limited to: • Acute macular neuroretinopathy (also known as acute macular outer retinopathy) • Autoimmune / Immune-mediated retinopathy • Autoimmune / Immune-mediated uveitis, including idiopathic uveitis and sympathetic ophthalmia • Cogan's syndrome: an oculo-audiovestibular disease • Ocular pemphigoid • Ulcerative keratitis • Vogt-Koyanagi-Harada disease
Gastrointestinal disorders	
Autoimmune / Immune-mediated pancreatitis	
Celiac disease	
Inflammatory Bowel disease	Including but not limited to: • Crohn’s disease • Microscopic colitis • Terminal ileitis • Ulcerative colitis • Ulcerative proctitis
Hepatobiliary disorders	
Autoimmune cholangitis	
Autoimmune hepatitis	
Primary biliary cirrhosis	
Primary sclerosing cholangitis	
Musculoskeletal and connective tissue disorders	
Gout	• Includes gouty arthritis
Idiopathic inflammatory myopathies	Including but not limited to: • Dermatomyositis • Inclusion body myositis • Immune-mediated necrotizing myopathy • Polymyositis

Medical Concept	Additional Notes
Mixed connective tissue disorder	
Polymyalgia rheumatica (PMR)	
Psoriatic arthritis (PsA)	
Relapsing polychondritis	
Rheumatoid arthritis	Including but not limited to: • Rheumatoid arthritis associated conditions • Juvenile idiopathic arthritis • Palindromic rheumatism • Still's disease • Felty's syndrome
Sjögren's syndrome	
Spondyloarthritis	Including but not limited to: • Ankylosing spondylitis • Juvenile spondyloarthritis • Keratoderma blenorrhagica • Psoriatic spondylitis • Reactive Arthritis (Reiter's Syndrome) • Undifferentiated spondyloarthritis
Systemic lupus Erythematosus	• Includes Lupus associated conditions (e.g., Cutaneous lupus erythematosus, Lupus nephritis, etc.) or complications such as shrinking lung syndrome (SLS)
Systemic Scleroderma (systemic sclerosis)	• Includes Reynolds syndrome (RS), systemic sclerosis with diffuse scleroderma and systemic sclerosis with limited scleroderma (also known as CREST syndrome)
Neuroinflammatory/neuromuscular disorders	
Acute disseminated encephalomyelitis (ADEM) and other inflammatory demyelinating variants	Includes the following: • Acute necrotizing myelitis • Bickerstaff's brainstem encephalitis • Disseminated necrotizing leukoencephalopathy (also known as Weston-Hurst syndrome, acute hemorrhagic leuko-encephalitis, or acute necrotizing hemorrhagic encephalomyelitis) • Myelin oligodendrocyte glycoprotein antibody-associated disease • Neuromyelitis optica (also known as Devic's disease) • Noninfective encephalitis / encephalomyelitis / myelitis • Postimmunization encephalomyelitis
Guillain-Barré syndrome (GBS)	• Includes variants such as Miller Fisher syndrome and the acute motor and sensory axonal neuropathy (AMSAN)
Idiopathic cranial nerve palsies/paresis and inflammations (neuritis)	Including but not limited to: • Cranial nerve neuritis (e.g., Optic neuritis) • Idiopathic nerve palsies/paresis (e.g., Bell's palsy) • Melkersson-Rosenthal syndrome • Multiple cranial nerve palsies/paresis
Multiple sclerosis (MS)	Includes the following: • Clinically isolated syndrome (CIS) • Malignant MS (the Marburg type of MS) • Primary-progressive MS (PPMS) • Radiologically isolated syndrome (RIS) • Relapsing-remitting MS (RRMS) • Secondary-progressive MS (SPMS) • Uhthoff's phenomenon
Myasthenia gravis	• Includes ocular myasthenia and Lambert-Eaton myasthenic syndrome
Narcolepsy	• Includes narcolepsy with or without presence of unambiguous cataplexy

Medical Concept	Additional Notes
Peripheral inflammatory demyelinating neuropathies and plexopathies	Including but not limited to: • Acute Brachial Radiculitis (also known as Parsonage-Turner Syndrome or neuralgic amyotrophy) • Antibody-mediated demyelinating neuropathy • Chronic idiopathic axonal polyneuropathy (CIAP) • Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP), including atypical CIDP variants (e.g., multifocal acquired demyelinating sensory and motor neuropathy also known as Lewis-Sumner syndrome) • Multifocal motor neuropathy (MMN)
Transverse myelitis (TM)	• Includes acute partial transverse myelitis (APTM) and acute complete transverse myelitis (ACTM)
Renal disorders	
Autoimmune / immune-mediated glomerulonephritis	Including but not limited to: • IgA nephropathy • IgM nephropathy • C1q nephropathy • Fibrillary glomerulonephritis • Glomerulonephritis rapidly progressive • Membranoproliferative glomerulonephritis • Membranous glomerulonephritis • Mesangioproliferative glomerulonephritis • Tubulointerstitial nephritis and uveitis syndrome
Skin and subcutaneous tissue disorders	
Alopecia areata	
Autoimmune / immune-mediated blistering dermatoses	Including but not limited to: • Bullous Dermatitis • Bullous Pemphigoid • Dermatitis herpetiformis • Epidermolysis bullosa acquisita (EBA) • Linear IgA-mediated bullous dermatosis (LABD), also known as Linear IgA disease • Pemphigus
Erythema multiforme	
Erythema nodosum	
Reactive granulomatous dermatitis	Including but not limited to • Interstitial granulomatous dermatitis • Palisaded neutrophilic granulomatous dermatitis
Lichen planus	• Includes liquen planopilaris
Localized Scleroderma (Morphoea)	• Includes Eosinophilic fasciitis (also called Shulman syndrome)
Psoriasis	
Pyoderma gangrenosum	
Stevens-Johnson syndrome (SJS)	Including but not limited to: • Toxic Epidermal Necrolysis (TEN) • SJS-TEN overlap
Sweet's syndrome	• Includes Acute febrile neutrophilic dermatosis
Vitiligo	
Vasculitis	
Large vessels vasculitis	Including but not limited to: • Arteritic anterior ischemic optic neuropathy (AAION or arteritic AION) • Giant cell arteritis (also called temporal arteritis) • Takayasu's arteritis

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

8.4.4.2. Other AEs of special interest

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/AESI

- 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 10.3.5.7
- 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.

Table 17 Timeframes for submitting SAE, pregnancy and other events reports to GSK

Type of event	Initial reports		Follow up of relevant information on a previous report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours*‡	paper/electronic Adverse Events Report	24 hours*	paper/electronic Adverse Events Report
Pregnancies	24 hours*	paper pregnancy notification report/electronic pregnancy report	24 hours *	paper pregnancy follow up report/electronic pregnancy report
AESIs	24 hours**‡	paper/electronic Adverse Events Report	24 hours*	paper/electronic Adverse Events Report

* Timeframe allowed after receipt or awareness of the information by the investigator/site staff.
**Timeframe allowed once the investigator determines that the event meets the protocol definition of an AESI
‡ Paper Adverse Events 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.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.4.6. Pregnancy

Female participants who become pregnant after administration of the study intervention may continue the study at the discretion of the investigator.

- Details of all pregnancies in female participants will be collected after the start of study intervention and until the last visit (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 participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on the participant and the neonate and the information will be forwarded to the sponsor. See Table 17 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 post-dosing 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 holding rules

Table 18 Contact information for reporting SAEs, AESIs, pregnancies and study holding rules

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** holding/stopping **rules** If a holding/stopping rule is met, the investigator must immediately inform the GSKs 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	**Back up study contact for escalation of** holding/stopping **rules** Refer to the local study contact information document.

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 part of 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.

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

PK 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

Section is not applicable.

8.9. Immunogenicity assessments

Immunogenicity is described in Section 8.2

8.10. Health economics

CCI

[redacted]

CCI [redacted]

9. STATISTICAL CONSIDERATIONS

The statistical analysis plan will be finalized prior to the first subject 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, i.e., the primary 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% CIs.

9.2. Analysis sets

Analysis set	Description
Screened	All participants who were screened for eligibility
Enrolled	All participants who entered the study (who were randomized or received study intervention or underwent a post-screening 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
Exposed Set (ES)	All participants who received a study intervention. Analysis per group is based on the study intervention administered
Per Protocol Set (PPS)	All eligible participants who received the dose of study intervention as per protocol, had immunogenicity results pre- and Day 29 post-dosing, without intercurrent conditions (influenza disease) that may interfere with immunogenicity and without prohibited concomitant medication/vaccination before Day 29. The analysis will be done according to the study intervention that participants received. Results from blood sample deviating from the dosing/blood draw intervals (refer to Table 3 and Table 4) as well as results obtained after intercurrent conditions (influenza disease***, new malignancy and immunocompromised condition***) that may interfere with immunogenicity or after prohibited concomitant medication/vaccination during this period will be excluded from the PPS.

9.3. Statistical analyses

The co-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 ES. All analyses will be done separately for OAs and YAs according to study phase, unless specified otherwise.

9.3.1. Co-primary reactogenicity and safety endpoints

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

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-Day 28 post-dosing) with its exact 95% confidence interval (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 MAE and with at least 1 report of AESI, respectively, classified by the MedDRA SOC and PT and reported from Dose 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 - Day 28 post-dosing) will be summarized by group.

9.3.1.1. Analysis of reactogenicity: Bayesian Logistic Regression Model (BLRM)

An adaptive BLRM will be used to inform on the posterior probability of the true Grade 3 solicited event rate for all dose levels used in Phase 1 study groups. The use of Bayesian response adaptive models for Phase 1 studies has been advocated by the European Medicines Agency (EMA) adopted guideline on small populations [EMA, 2006] and by Rogatko et al. [Rogatko, 2007] and is one of the key elements of the FDA's Critical Path Initiative.

The 2-parameter BLRM described by Neuenschwander et al., 2008 [Neuenschwander, 2008] will be used to assess reactogenicity and recommend the mRNA doses to proceed to Phase 2 of the study.

Standardized dose level will be used such that one of the doses (d*) equals 1, e.g., doses are rescaled as d/d*. Consequently, α is equal to the odds of the probability of intolerance at d*. This model was shown to be fit for purpose in the context of Phase 1 mRNA vaccine dose range [Walsh, 2020; Kremsner, 2021]. The prior distribution will be updated after each group of participants with all the data available in the Safety Set from the current study. Once updated, the distribution summarizes the posterior probability that the true Grade 3 solicited event rate for each dose level lies in the following categories:

- 0% to <18%: targeted tolerance; and

- ≥18% to 100%: intolerance.

The principle of the BLRM mandates that any dose of the study vaccine candidates that has more than a 50% chance of being in the intolerance category is not considered for the next dose administrations [Neuenschwander, 2008; Babb, 1998].

Section 10.7 provides additional details on the model and data scenarios.

A clinical synthesis of the available safety and reactogenicity information (including symptoms that are not Grade 3), and, if available, laboratory values as well as the recommendations from the Bayesian model and the ***SRT/iSRC*** or iDRC (Refer to Section 10.1.6 for the ***SRT, iSRC*** and iDRC roles) will be used to select the investigational study intervention for Phase 2. The frequency of each safety event associated to holding rules (see Table 13) will be tabulated by study group (i.e., by dose level and formulation). Individual data will also be available.

9.3.2. Co-primary and secondary immunogenicity endpoints

At each phase, the group difference between the investigational study intervention formulation, and dose level and the control group will be assessed separately as follows for CCI [redacted]:

- At each post-dosing timepoint separately, the 2-sided CI for group GMT ratio between investigational study intervention dose and (over) the control 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 control group), actual age of participants, country, flu vaccination history and $\log_{10}$-transformed concentration 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. Concentrations below the assay lower level of quantification (LLOQ) will be replaced by half the assay LLOQ.
- For a given age group, the 2-sided 95% CI on group difference in SCR between an investigational study intervention and (minus) the control group will be computed at Day 29 based on the method of Miettinen and Nurminen [Miettinen, 1985].
- For CCI [redacted] only: the percentage of participants achieving seroprotection, defined as having post-dosing CCI [redacted] will be summarized by age group with associated exact 95% CI.

All analyses will be performed separately for each age group, where applicable.

Abbreviation/term	Definition
GMI	The geometric mean of the ratios of the post-dosing titer over the Day 1 titer.
CCI	The percentage of dosed participants who have either a CCI pre-dose CCI and a post-dosing CCI or a pre-dose CCI and at least a 4-fold increase in post-dosing CCI.
	The percentage of dosed participants who have either a CCI pre-dose CCI and a post-dosing CCI or a pre-dose CCI and at least a 4-fold increase in post-dosing NI titer.
SPR (seroprotection rate)*	The percentage of dosed participants with a CCI.
S+ (seropositive)	Titer ≥LLOQ

CCI

9.4. Interim analyses

9.4.1. Sequence of interim and other planned analyses

In addition to the analyses detailed below, additional analyses e.g., safety analyses, may be conducted to support the ***SRT***, iSRC and iDRC decisions, as described in Section 8.3.7.1. Refer to Section 10.1.6 for the ***SRT***, iSRC and iDRC roles.

Two interim analyses are foreseen and will be conducted upon availability of all primary endpoints up to Day 29 for participants in Phase 1 and Phase 2, respectively. CCI . ***For the observer-blinded Phase 2 interim analyses, 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 group data 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.***

An 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. This may be performed separately for each phase.

Analysis of tertiary endpoints may be performed at a later stage. Tertiary analyses deemed futile due to the other study results will not be analyzed nor reported.

9.4.2. Statistical considerations associated with the interim analyses

As this study is descriptive and each analysis will be completed on expected final immunogenicity data, there will be no type I error adjustment for the different analyses. All interim analyses will be based on the ES.

9.5. Sample size determination

Enrolled participants who withdraw from the study will not be replaced.

9.5.1. Sample size determination for Phase 1

The study is designed to provide a reasonable precision for the rate of Grade 3 solicited events and to describe the safety profile of an mRNA-based vaccine.

For each investigational study intervention group, it is expected that 24 participants will be enrolled. Assuming a maximum acceptable rate of Grade 3 solicited events of 18%, it is possible to calculate the probability of a lower true Grade 3 solicited event rate given a different number of participants with Grade 3 solicited event(s). Table 19 provides the estimate and 95% credibility interval for a given observed number of participants for a sample size of 24 participants per study group (assuming a Beta [0.5,0.5] prior distribution). For example, if 4 participants report Grade 3 solicited event(s) among 24 exposed participants, the posterior probability that the true Grade 3 solicited event rate is <18% is 54.5%.

Table 19 Posterior probability estimates of Grade 3 solicited event rate <18% for different observed numbers of participants with Grade 3 solicited event(s) and 95% credibility interval for the rate

Number of participants with Grade 3 solicited event(s)	Estimate (95% credibility interval) in %	Probability Grade 3 solicited event rate <18%
0	2 (0 - 9.8)	99.8
1	6 (0.5 - 17.9)	97.6
2	10 (1.8 - 24.1)	89.9
3	14 (3.6 - 29.7)	74.8
4	18 (5.9 - 34.9)	54.5

A further description of the BLRM, including prior, hypothetical data scenarios of number of Grade 3 solicited events that could occur in the actual study, and the decision guides are presented in Section 10.7.

9.5.2. Sample size determination for Phase 2

The primary objective is to explore how the different formulation(s) or dose level(s) of mRNA-based vaccine compare to licensed control group(s).

The sample size of ***108*** 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 below 12% for difference in seroconversion rates for the different strains (Table 20) and a 95% CI with an expected half-width of ***1.36*** fold for the group geometric mean concentration ratio considering a population standard deviation of ***0.5*** in $\log_{10}$ transformation concentration post-dosing and 5% of unevaluable participants per group.

Table 20 Half-width of 95% CI for the group difference in seroconversion rates by to control and strain (Evaluable N per group = *108*)

Control	Strain	Proportion (%)*	95% CI of Proportion (%)	*Lower* Half-width of 95 CI (%)
CCI [redacted]				

*Obtained from meta-analysis of historical data from CCI [redacted]

CCI [redacted].

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 (CIOMS) 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.
- As per local regulations, amendments to the protocol may require IRB/IEC approval before implementation of changes made to the study design. Changes necessary to eliminate an immediate hazard to study participants may be implemented prior to IRB/IEC approval.
- Protocols and substantial amendments to the protocol may require health authority approval prior to initiation and/or implementation as per local regulations. Changes necessary to eliminate an immediate hazard to study participants may be implemented prior to health authorities approval.

- 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, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing new 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, Health Insurance Portability and Accountability Act (HIPAA) requirements, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- 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.
- Participants who are rescreened are required to sign a new ICF, only if there are changes to the original ICF. If there are no changes to the original ICF, participants should confirm that they still agree to be part of the study. This information should be captured in the participant source document.

The ICF will contain a separate Section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will

explain to each participant the objectives of the exploratory 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 such as date of birth, sex of the baby will be collected as part of safety follow up. Consent for 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.

Refer to Section 8.3.7.1 for details on enrollment strategy for Phase 1 (including enrollment of sentinel and non-sentinel participants) and Phase 2.

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 electronic 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. Their data to 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 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.

10.1.6. Committees structure

The internal ***SRT*** is a cross-functional team including safety, clinical, and statistics experts from both GSK and CureVac. The ***SRT*** includes study/project team members. The ***SRT*** is responsible for the ongoing assessment of benefit-risk for the investigational study intervention. The role of the ***SRT*** is to oversee the safety of participants and study conduct in both Phase 1 (unblinded) and Phase 2 (blinded).

The iSRC is a cross-functional team including safety, clinical, and statistics experts from GSK. The iSRC members are independent of the study/project team. The role of the iSRC is to oversee the safety of participants and study conduct in Phase 2 (unblinded).

The iDRC is a multidisciplinary committee including immunogenicity, safety, clinical, and statistics experts from GSK. The iDRC members are from the sponsor therapeutic-area leadership. The role of the iDRC is to oversee interim analyses in both Phase 1 and Phase 2, and to determine the composition of the investigational study intervention formulations to be assessed Phase 2. Refer to Section 4.3 for detailed information.

For more details, refer to iDRC and iSRC charters, ***SRT*** framework or relevant procedure.

10.1.7. Dissemination of clinical study data

- The key design elements of this protocol and results summaries will be posted on EU clinical trials Register, www.ClinicalTrials.gov and/or GSK Clinical 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. Where external regulations require earlier disclosure or allow for delaying 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 plain language summary with the study participants, as appropriate. The full study report will be made available upon request, after decision on marketing authorization by regulatory authorities.
- 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.

10.1.8. Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs 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 CRF.
- 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.
- QTLs will be predefined in the QTL Report to identify systematic issues that can impact participant 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 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), methods, responsibilities, and requirements, including handling of noncompliance 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 25 years from the issue of the final CSR/ equivalent summary unless local regulations or institutional policies require a different retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.9. Source documents

- 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.

- 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

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

The results of this study may be published in peer reviewed scientific literature and/or presented at scientific meetings. The sponsor will comply with the requirements for publication of study results in accordance with standard editorial and ethical practice and as per the sponsor's internal policy. Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.2. Appendix 2: Clinical laboratory tests

10.2.1. Protocol-required safety laboratory assessments

- The tests detailed in Table 21 will be performed by the local laboratory using local standards, and the results will be encoded by the investigator into the eCRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report.

Laboratory data will be graded according to the FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adults and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" dated September 2007. These laboratory values serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate. Refer to Section 10.2.2 for more information on toxicity grading scales to be considered in this study.

Table 21 Protocol-required safety laboratory tests (Phase 1 only)

Assay type	System	Component	Method
Hematology	Whole Blood	White Blood Cells count and differentials	As per local laboratory procedures
	Whole Blood	Erythrocytes	
	Whole Blood	Hemoglobin	
	Whole Blood	Glycated hemoglobin (Hba1c) *	
	Whole Blood	Platelets	
Biochemistry	Serum	Blood urea nitrogen/Urea	
		Creatinine	
		Alanine aminotransferase (ALT)	
		Aspartate aminotransferase (AST)	
		Troponin (Troponin I and/or Troponin T)	
Urinalysis[*, **]	Urine	Leukocytes, Blood, Proteins, Glucose, Ketones, Bilirubin, Urobilinogen, Nitrite, Specific gravity, pH	

* Only applicable for screening visit in Phase 1.
** Urinalysis will be done by dipstick.

10.2.2. FDA Guidance for industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials (September 2007)

The laboratory values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Table 22 Toxicity grading scales for biochemistry parameters evaluated in the current study (adapted from FDA Guidance for industry)

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN

ULN is the upper limit of the normal range.
* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as potentially life-threatening (Grade 4). For example, a low sodium value that falls within a Grade 3 parameter (125-129 mE/L) should be recorded as a Grade 4 hyponatremia event if the participant had a new seizure associated with the low sodium value.

Table 23 Toxicity grading scales for hematology parameters evaluated in the current study (adapted from FDA Guidance for industry)

Hematology *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 –10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10 800 – 15 000	15 001 – 20,000	20 001 – 25 000	> 25 000
WBC Decrease - cell/mm^3	2 500 – 3 500	1 500 – 2 499	1 000 – 1 499	< 1 000
Lymphocytes Decrease - cell/mm^3	750 – 1 000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1 500 – 2 000	1 000 – 1 499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1 500	1 501 – 5 000	> 5 000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125 000 – 140 000	100 000 – 124 000	25 000 – 99 000	< 25 000

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

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).

  The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. "Lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

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 (>35% direct bilirubin) or international normalized ratio (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 events 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 24 Solicited administration site events

Pain at administration site
Redness at administration site
Swelling at administration site
Lymphadenopathy*

* 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 25 Solicited systemic events

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

Note: Participants will be instructed to measure and record the axillary 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.

Site staff should monitor participants compliance to completion of eDiary on ongoing basis based on eDiary web-reporting portal and/or automated alerts sent by e-mail. During solicited reporting period, if eDiary was not submitted by a participant for a day, site should attempt to contact the participant as quickly as possible, ideally the following day, to retrain on importance of eDiary compliance and collect missing information, the data for the missed eDiary for that day will be documented in the participant's records and entered into eCRF.

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 participants who has signed the informed consent or through his/her caregiver. Unsolicited AEs include both serious and non-serious 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). Upon notification from eDiary system to the investigator of the occurrence of unsolicited AEs that are medically attended or perceived as a concern by the participant, the site should contact the participant to collect the safety information as soon as possible. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records ***and entered into eCRF***. • Unsolicited AEs that are not medically attended nor perceived as a concern by the participant will be collected during an interview with the participant and by review of available medical records at the next visit/contact ***and documented in the participant's records and entered into eCRF***. • ***Site staff should monitor participants compliance to completion of eDiary on ongoing basis based on eDiary web-reporting portal and/or automated alerts sent by e-mail. During unsolicited reporting period, if eDiary was not submitted by a participant for a day, site should attempt to contact the participant in timely manner to re-train on importance of eDiary compliance and to collect information about AEs, if any.***

10.3.5. Recording, assessment and follow up of AE, SAE, 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 number, 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 (provided by Signant Health) will be used in this study to capture solicited administration site or systemic events and inform the site staff of the occurrence of an unsolicited event. The participant/caregiver 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 AEs was not possible for any reasons via the eDiary and solicited AEs were reported to the investigator by the participant/caregiver, 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.

eDiary device should be returned to the site after the end of the relevant data collection period on Day 29 (Visit 4). If eDiary application was installed on participant's own device, it must be uninstalled after Day 29. Any unreturned eDiary will be sought from the participant through telephone call(s) or any other convenient procedure.

10.3.5.2. Time period for collecting and recording AEs, SAEs, AESIs and pregnancies

Occurrence of unsolicited events will be recorded in to eDiary within 28 days after administration of the study intervention (Day 1 to Day 28). An automatic reminder to complete the eDiary will be sent to the participants/caregivers during this timeframe. Unsolicited AE information must 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.

All solicited events that occur during 7 days following administration of the dose of study intervention (Day 1 to Day 7 included) must be recorded into the eDiary, irrespective of intensity. Solicited events ongoing after Day 7 will continue to be recorded into the eDiary from Day 8 to Day 28 and followed-up until the event has resolved, subsided, stabilized, disappeared, or until the event is otherwise explained, the participant is lost to follow up, or study is completed.

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.

Refer to Section 8.4.1 for more information on collection and reporting of safety information in this study.

10.3.5.3. Assessment of intensity

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

Table 26 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*	0	< 25 mm
	1	≥ 25 - ≤ 50 mm
	2	≥ 51 - ≤ 100 mm
	3	> 100 mm
Swelling at administration site*	0	< 25 mm
	1	≥ 25 - ≤ 50 mm
	2	≥ 51 - ≤ 100 mm
	3	> 100 mm
Lymphadenopathy**	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
Temperature***	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	≥ 39.0°C (102.1°F)
Headache	0	None
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	None
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Myalgia	0	None
	1	Mild: Myalgia present but does not interfere with activity
	2	Moderate: Myalgia that interferes with normal activity
	3	Severe: Myalgia that prevents normal activity
Arthralgia	0	None
	1	Mild: Arthralgia present but does not interfere with activity
	2	Moderate: Arthralgia that interferes with normal activity
	3	Severe: Arthralgia that prevents normal activity

Event	Intensity grade	Parameter
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

* Greatest surface diameter in mm
** Defined as localized axillary, cervical or supraclavicular swelling or tenderness ipsilateral to the administration arm
*** Refer to the SoA (Section 1.3) for the definition of fever and the preferred location for temperature measurement.

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 adverse event 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 adverse event 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 adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

10.3.5.4. Assessment of causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/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 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 an SAE follow up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.3.5.5. Assessment of outcomes

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

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

10.3.5.6. 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.
- 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 non-serious 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 non-serious AEs must be followed for 6 months (until Day 183) or until the participant is lost to follow up.

Follow up during the study

AEs/AESIs documented at a previous visit/contact and defined as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the end of the study (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 post-mortem 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 Adverse Events Report if applicable. Generally, the follow up period does not need to be longer than 6 to 8 weeks after the estimated date of delivery.

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

Furthermore, 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 10.3.6.

10.3.5.7. 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 (refer to Section 8.4.3).

10.3.6. 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 becomes aware of any serious, non-serious AEs, pregnancy exposure, related to any GSK non-IMP they will report these events to GSK or to the concerned competent authority 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.

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. Woman of childbearing potential (WOCBP)

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

1. Adolescents of childbearing potential: Tanner stage ≥2 (post-thelarche) irrespective of the occurrence of menarche or following menarche.
2. 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. Woman of non-childbearing potential (WONCBP)

Women in the following categories are considered WONCBP:

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

3. Postmenopausal female

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

- A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than 1 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 27).

Table 27 Highly effective contraceptive methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • Injectable • Oral (if allowed by local regulation or if it is part of standard medical practice in the country)
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion/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 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 study and the preferred and usual lifestyle of the participant.)*

[a] `Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects 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 adverse event 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 adverse device effect 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 adverse device effect 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 AE and/or SAE 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 number, 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, non-serious incident (including device deficiencies and malfunctions) related to any GSK non-IMP product they will report these events to GSK or to the concerned competent authority via the national spontaneous reporting system. These will be classified as spontaneous ICSRs.

10.5.4.2. Assessment of intensity

Refer to Section 10.3.5.3

10.5.4.3. Assessment of causality

Refer to Section 10.3.5.4

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 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 table) or to the medical monitor by telephone.
- If the site during the course of the study or post-study becomes aware of any serious, non-serious AEs, pregnancy exposure, related to any GSK device they will report these events to GSK or to the concerned competent authority 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 non-serious 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. Refer to 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: Country-specific requirements

10.6.1. *Specific requirements for South Africa*

As per regulatory requirement and due to high prevalence of HIV infection, all participants from South Africa with unknown HIV status (unknown or previously tested negative) will be counselled and tested for HIV infection, using the South African Health Products Regulatory Authority (SAHPRA) approved test kits prior to enrolment. If HIV result is positive, these participants will be excluded as per Section 5.2.1 Medical Conditions exclusion criterion 2.

Participants from South Africa with known HIV status (previously tested positive) 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/mm³ and their viral load has been undetectable (i.e., HIV-RNA <50 copies/mL). The evaluation will be made based on medical records, and no additional laboratory testing is required for known HIV positive participants.

10.7. Appendix 7 Statistics: BLRM Model specification and data scenarios

An adaptive BLRM will be used to inform on the posterior probability of the true Grade 3 solicited event rate for all mRNA dose levels used in Phase 1 study in order to recommend the mRNA doses to proceed to Phase 2 of the study:

$\text{logit}(p(d)) = \log(\alpha) + \beta_1 * \log(d/d^*)$

where

- $p(d)$ = percentage of participants with Grade 3 solicited event at mRNA dose level d
- $\text{logit}(p) = \log(p/(1-p))$
- $d^* = 50\mu g$ is the reference dose representing the total mRNA dose
- α is the intercept parameter
- β_1 is a dose effect

Since no prior information is available, the uncertainty about the dose-tolerance relationship (parameters α and β1) is expressed by a mixture of 2 bivariate normal distributions as follows:

- 80% weight for minimally informative component: $\log(\alpha) \approx$ normal (mean = -1.516, var = 1) and $\log(\beta_1) \approx$ normal (mean = -1.553, var=1), *a priori* assuming 10% and 18% Grade 3 solicited event rate at CCI [redacted], respectively.
- 20% weight for toxicity component: $\log(\alpha) \approx$ normal (mean = -0.708, var =1) and $\log(\beta 1) \approx$ normal (mean = -1.143, var = 1), *a priori* assuming 15% and 33% Grade 3 solicited event rate at CCI [redacted], respectively.

A zero covariance between priors is assumed.

A greater than 50% posterior probability that the Grade 3 solicited event rate ≥18% at a given mRNA dose will indicate that the dose may not be tolerable.

Hypothetical scenarios illustrating the posterior probability are presented in Table 28.

Table 28 Hypothetical data scenarios for assessment of reactogenicity using BLRM in YAs

Scenario	Age group	mRNA Dose	#Events	#Participants	CD – P(TD)	CD – P(OD)
1	YA	CCI	0	24	0.995	0.005
			0	24	1	0
			0	24	1	0
			0	24	1	0
			0	24	1	0
2	YA		0	24	0.995	0.005
			1	24	0.997	0.003
			1	24	0.998	0.002
			3	24	0.961	0.039
			5	24	0.758	0.242
3	YA		0	24	0.995	0.005
			0	24	1	0
			2	24	0.994	0.006
			4	24	0.834	0.166
			6	24	0.404	**0.596***

* Unacceptable reactogenicity, i.e., CD – P(OD) >0.5
CD = Current dose; P(TD) = Probability of tolerable dose; and P(OD) = Probability of overdose; YA: younger adult.

10.8. Appendix 8: Protocol amendment history

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

Amendment 1 (07 April 2023)

This amendment is considered substantial based on the criteria defined in EU Clinical Trial Regulation No 536/2014 of the European Parliament and the Council of the European Union because it significantly impacts the safety of participants.

Overall rationale for Amendment 1:

Following the feedback received from the Belgian and US Competent Authorities after the CTA and IND submission of the Flu SV MRNA-002 study, the protocol has been amended to accommodate requested clarifications.

Summary of changes table of previous amendments:

Section # and title	Description of change	Brief rationale
LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS	Definition of adverse event of special interest (AESI) was added.	To comply with the recommendation from the Belgian Competent Authorities.
1.2. Schema 8.3.7.1.1. Phase 1 8.3.7.1.3. Phase 2 (OA groups)	Follow up period for sentinel participants was extended to 7 days after dosing (i.e., Day 1 to Day 8 post-dosing).	To comply with the recommendation from the US Competent Authorities.
1.3. Schedule of activities (SoA) (Table 2) Table 5 Objectives and endpoints 8.2.2. Laboratory assays Table 11 Laboratory assays	Wording related to the generation of monoclonal antibodies was removed.	To comply with the recommendation from the Belgian Competent Authorities.
2.3.1. Risk assessment	Footnote related to myocarditis/pericarditis surveillance was added.	To comply with the recommendation from the Belgian Competent Authorities.
4.1. Overall design Table 8 Study intervention(s) administered. Phase 1 9.5.1. Sample size determination for Phase 1	Wording related to the number of groups in Phase 1 and approximate number of participants in both phases was updated.	To comply with the recommendation from the Belgian Competent Authorities.
4.2.1. Rationale for study design of Phase 1 4.2.2. Rationale for study design of Phase 2	Mention of maximum number of sentinel participants across sites was added.	To comply with the recommendation from the Belgian Competent Authorities.
4.2.1. Rationale for study design of Phase 1 4.3.1. Dose selection for Phase 1	Wording for justification of dose selection of individual antigens was updated.	To comply with the recommendation from the Belgian Competent Authorities.
5.2.1. Medical conditions	Exclusion criterion N°8 was updated to clarify that participants with conditions that moderately or severely impair cognition will be excluded from the study, not only conditions that may interfere with the completing of study tasks.	To comply with the recommendation from the Belgian Competent Authorities.
8.2.3. Immunological read-outs Table 12 Immunological read-outs	Footnote related to the number of participants was updated.	To align with recommendations from Belgian Competent Authorities.
8.3.4. Myocarditis and pericarditis assessment and definitions	Bullet point classifying asymptomatic participants as suspected cases was removed.	The definition of a suspected case of myocarditis/pericarditis has been updated to align with

Section # and title	Description of change	Brief rationale
		the definition of a probable case by the Brighton Collaboration (SPEAC, 2022) and the CDC (CDC, 2021).
8.3.7.1.1. Phase 1 8.3.7.1.3. Phase 2 (OA groups)	Maximum number of sentinel participants to be dosed per day was specified.	To comply with the recommendation from the Belgian Competent Authorities.
Table 13 Study holding rules	Study holding rule 1f has been updated. Holding rules 2a and 2b were made applicable for Phase 2 participants.	To comply with the recommendation from the US Competent Authorities.
9.5.1. Sample size determination for Phase 1	Number of participants per group was further clarified.	To comply with the recommendation from the Belgian Competent Authorities.
10.2.2. FDA Guidance for industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials (September 2007)	Tables 21 and 22 were updated to remove the values corresponding to SI units.	To align with original FDA definitions.
10.3.5.1. AE and SAE recording	Name of the third-party provider for the eDiary was added.	To address EMA inspection finding in another study conducted by GSK.

Details of substantial changes made to the study protocol since the previous submitted version are provided in the Protocol Amendment Substantial Change Table accompanying this protocol amendment.

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